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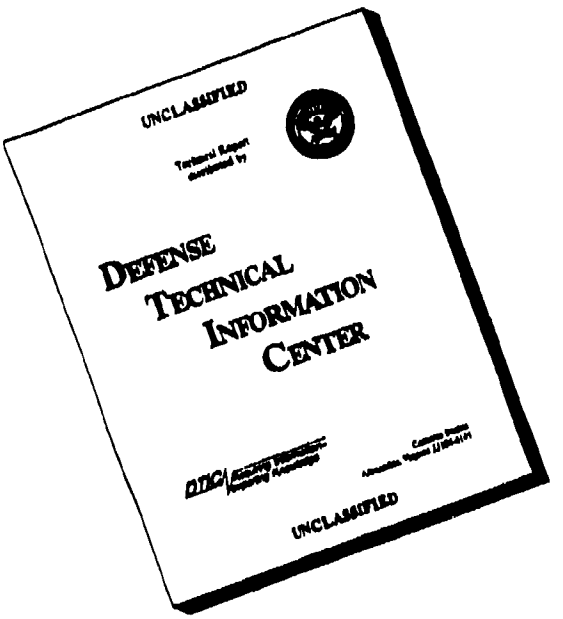

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Preformulation Studies of Selected Pretreatment and Therapeutic Compounds

Annual Progress Report
July 1, 1982 to June 30, 1983

John L. Lach
Douglas R. Flanagan
Lloyd E. Matheson, Jr.

July, 1983

Supported by

U.S. Army Medical Research and Development Command
Fort Detrick
Frederick, Maryland 21701-5012

Contract No. DAMD17-79-C-9136

College of Pharmacy
University of Iowa
Iowa City, Iowa 52242

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WR6026•2HCl; WR638; WR180,409•H_3PO_4; WR142,490•HCl; WR171,969•HCl; formycin 3,5' monophosphate; physicochemical properties; stability; preformulation; capsule production; tablet production; placebo; liposomes; antimalarials; anti-leishmaniasis

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The annual report contains:

1. Resume' of progress
2. Quarterly Report No. 12 (1July1982-30Sep1982)
3. Quarterly Report No. 13 (1Oct1982-31Dec1982)
4. Quarterly Report No. 14 (1Jan1983-31Mar1983)
5. Quarterly Report No. 15 (1Apr1983-30June1983)

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SUMMARY

This annual report represents preformulation and formulation and production projects conducted in the fourth year of this contract on the following drugs:

WR6026·2HCl

WR638

WR180,409·H_3PO_4

WR142,490·HCl

WR171,669·HCl

Formycin B,5' Monophosphate.

This work consists of the physicochemical characterization of WR6026·2HCl including stability studies; formulation and production of WR638 capsules; formulation and production of WR180,409·H_3PO_4 tablets and matching placebos; coating of WR142,490·HCl tablets and formulation and production of matching placebos; the preparation of capsules containing ^{14}C labelled WR171,669·HCl with polyvinylpyrrolidone; and the development of liposomes containing formycin B,5' monophosphate.

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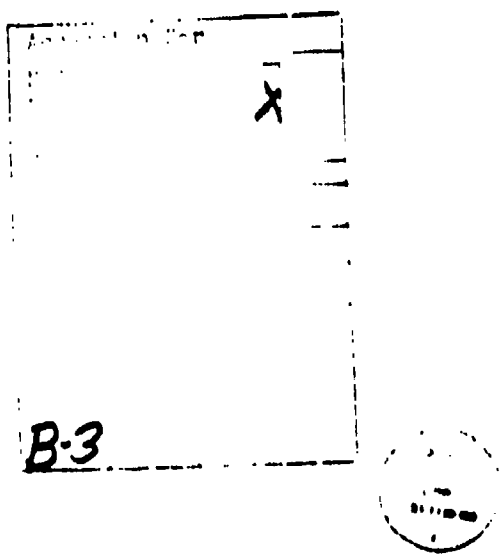

RESUME' OF PROGRESS

Preparation of Capsules Containing ^{14}C-Labelled WR171,669·HCl Formulations with PVP

To determine whether the enhancements in dissolution rate observed with PVP coprecipitates of WR171,669·HCl would result in better bioavailability, capsule formulations were prepared for *in vivo* evaluation. A limited number (8) of capsules were prepared containing 100 mg of WR171,669·HCl physically mixed with 300 mg of PVP (C-15) and a limited number (8) of capsules containing 100 mg of WR171,669·HCl coprecipitated from ethanol with 300 mg of PVP (C-15). Since a reliable plasma assay was not available for these *in vivo* studies, ^{14}C-labelled WR171,669·HCl was incorporated into unlabelled WR171,669·HCl to permit blood level determinations by radio chemical methods.

To prepare these formulations, 55 mg was received (1.43 mCi) of ^{14}C-WR171,669·HCl (Lot #3959-41) from RTI. It was determined that 3.27 mg of labelled WR171,669·HCl would be required per capsule to ensure sufficient radioactivity in blood samples to be detectable. Theoretically, each capsule would contain 3.27 mg of labelled and 96.73 mg of unlabelled WR171,669·HCl and 300 mg of PVP (C-15). For coprecipitates it had been determined by thermogravimetric analysis that 4-5% residual solvent remained which would require an increase of 16-20 mg in the total capsule weight bringing the final weight to 416-420 mg/capsule.

To obtain enough coprecipitate for eight capsules, sufficient material was incorporated to obtain 8¼ capsules. The actual weights of each component are given below

	Weight
WR171,669·HCl (^{14}C)	0.027 g
WR171,669·HCl (BB43807) AGC-W100-2, 30Jan81)	0.799 g
PVP (Plasdone C-15)	2.476 g

These components were dissolved in a small volume of 95% ethanol (25-50 ml) in a 100 ml round bottom flask. The resulting solution was evaporated on a flash evaporator and the resulting coprecipitate was further dried in a vacuum desicator at 60°C. The coprecipitate was assayed for ^{14}C-WR171,669·HCl by weighing four separate samples, dissolving each in 10 ml of scintillation cocktail and counting in a Beckman LS-100 scintillation counter. Counting efficiency for each sample was determined using ^{14}C-toulene and was found to be 86-91%. The four samples gave 104.07%, 98.03%, 98.49% and 104.0% activity compared to theory for an average of

101.15%. The powdered coprecipitate was weighed out for each capsule and packed into a size 0 capsule.

To prepare a physical mixture of WR171,699·HCl with PVP, the ^{14}C-WR171,699·HCl (27 mg) was first mixed with unlabelled WR171,699·HCl (798 mg) by dissolving both in 95% ethanol and flash evaporating. The resulting powdered WR171,699·HCl was assayed for ^{14}C-activity by dissolving a weighed portion in scintillation cocktail and counting with a Beckman LS-100 scintillation counter. The activity of the labelled drug was found to be 91.6% of that calculated theoretically. No correction for this reduced activity was incorporated into the calculation of amounts to be used in the physical mixture since there was concern that there may not then be sufficient material for eight capsules. The ^{14}C-labelled WR171,669·HCl was mixed with sufficient PVP (Plasdone C-15) to give the same 1:3 weight ratio obtained with the coprecipitate. The two powders were mixed by geometric dilution with a glass mortar and pestle. The mixture was assayed by weighing three samples, dissolving in scintillation cocktail and counting with a Beckman LS-100 scintillation counter. Counting efficiency was determined for each sample with ^{14}C-toluene and was found to be 86-89%. The three samples gave 92.5%, 80.5% and 80.4% activity compared to theory for an average of 84.47%. The significantly lower activity is partially due to the powdered drug activity being 91.6% of theory and partially due to the difficulty in obtaining a homogeneous mixture by dry blending the powdered dry and PVP. Vigorous trituration could not be performed on the mixture because of the precautions taken to limit contaminating the work area with radioactive material. The powdered physical mixture was weighed out for each capsule and packed into a size 0 capsule.

Each capsule of coprecipitate and physical mixture were individually packaged in a separate vial, labelled with its weight and shipped by Federal Express to WRAIR for <u>in vivo</u> evaluation.

To correct for the differences in the coprecipitate activity compared to the physical mixture activity a factor of 1.1975 (101.15/84.47) should be used to multiply the physical mixture blood levels or conversely to divide the coprecipitate blood levels. With this correction the two formulations can then be properly compared on the basis of equivalent activity.

Development of Liposomes Containing Formycin B,5'-Monophosphate (FBMP)

The development of formycin B,5'-monophosphate-containing liposomes has been pursued during the last quarter of this budget year. It has been proposed that its toxicity may be significantly

reduced in liposomes and possibly an enhancement of activity against the Leishmania parasite may also be achieved.

Since formycin B,5'-monophosphate (FBMP) is rather expensive, it was recommended that initial development studies be conducted with inosine monophosphate (IMP) which is structurally similar to formycin B,5'-monophosphate (FBMP).

First, tonicity studies were conducted to determine the isotonic concentration of IMP by a freezing point depression method. The results are shown below:

Conc (mM)	Osmolatity (mOsm)
100	209
125	254
150	295

It was thus concluded that 150 mM is approximately isotonic, which for IMP as the disodium, heptahydrate salt (MW-518) is 77.7 mg/ml. This concentration was then employed in the swelling solution for the preparation of liposomes.

The UV spectral properties of IMP were also investigated since this method would be used for the assay of IMP entrapment. In aqueous solution and acidified isopropanol, the UV spectrum is slightly different. The results are summarized below:

Solvent	Wavelength (λ)	Molar absorptivity (ε)
Water	248 nm	11,950
Acidified Isopropanol	250 nm	10,330

On a mg/ml basis IMP as its disodium heptahydrate salt (IMP $Na_2 \cdot 7H_2O$) gives an absorbance of 23.07 (H_2O) or 20.00 (acidified isopropanol) at 1 mg/ml. Thus, the UV spectral methods are sufficiently sensitive to assay liposome entrapped IMP.

The following liposome formulation was employed for entrapping IMP:

DPPC	45 mg	to prepare 3 ml
Cholesterol	17.4 mg	of liposome dispersion
Vitamin E	0.258 mg	

Liposomes were prepared in the usual fashion by depositing the above lipid amounts on the wall of a 50 ml round bottom flask from a chloroform solution with a rotary evaporator, adding 3 ml of swelling solution containing 77.7 mg/ml IMP $Na_2 \cdot 7H_2O$ and mechanically shaking at 40°C until the lipid was completely removed from the flask wall. Entrapment was measured by

centrifugation of the liposomes and washing the liposome plug twice with normal saline to remove unentrapped IMP. The liposome plug was finally dissolved in isopropanol which had been acidified by adding 5 drops of concentrated HCl (the acid is required to dissolve IMP in isopropanol). The isopropanol solution is then assayed by UV spectral methods for IMP content. Assay of the whole liposome dispersion before washing gave 79.23 mg/ml for one preparation and 76.04 mg/ml and 76.34 mg/ml for a second preparation, which are reasonably close to the concentration of IMP $Na_2 \cdot 7H_2O$ put into the solution at the beginning of the swelling process. After washing, the entrapment for one preparation was 15.39% and for the second preparation (two measurements) was 13.05% and 13.26%. It thus appears that 13-16% of the IMP can be entrapped in this liposome preparation at isotonic concentrations of IMP. This entrapment level represents 10-12.5 mg is entrapped from a one milliliter solution at 77.7 mg/ml. Based upon the anhydrous salt (IMP Na_2, MW-392) this entrapment level is 7.5-9.5 mg from one milliliter a 59 mg/ml solution.

Leakage characteristics of IMP from these liposomes was studied at room temperature. One milliliter of washed liposomes in normal saline were placed in a dialysis sack (50,000 molecular weight cutoff) and dialyzed against normal saline. The dialyzate solution was periodically removed, replaced with fresh normal saline and assayed for IMP content by the UV spectral method. Below are the results of this leakage study:

Time (hr)	% Leakage
2	9.51
4	11.84
21	17.88
46	18.61
72	18.92
100	19.25

Compared to WR6026·2HCl the leakage of IMP is significantly reduced. Under equivalent conditions over 95% leakage of WR6026·HCl would be expected. At refrigerator temperature (4°C) the leakage rate is similar to that obtained at room temperature. The refrigerator leakage studies are being repeated to confirm this behavior.

We are now conducting identical entrapment studies with formycin B,5'-monophosphate, since we feel that we have learned as much as we need from the IMP studies.

QUARTERLY REPORT NUMBER 12

PREFORMULATION STUDIES FOR WR6026·2HCl

John L. Lach
Douglas R. Flanagan
Lloyd E. Matheson, Jr.

October, 1982

Supported by:

U.S. Army Medical Research and Development Command
Fort Detrick
Frederick, Maryland 21701-5012

Contract DAMD17-79-C-9136

College of Pharmacy
University of Iowa
Iowa City, Iowa 52242

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DATA SHEET SUMMARY

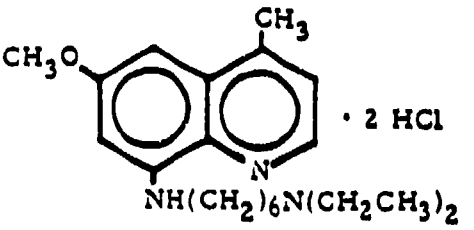
COMPOUND - WR6026·2HCl

LOT AF

BOTTLE NO. BK01845

MOLECULAR WEIGHT 416.44

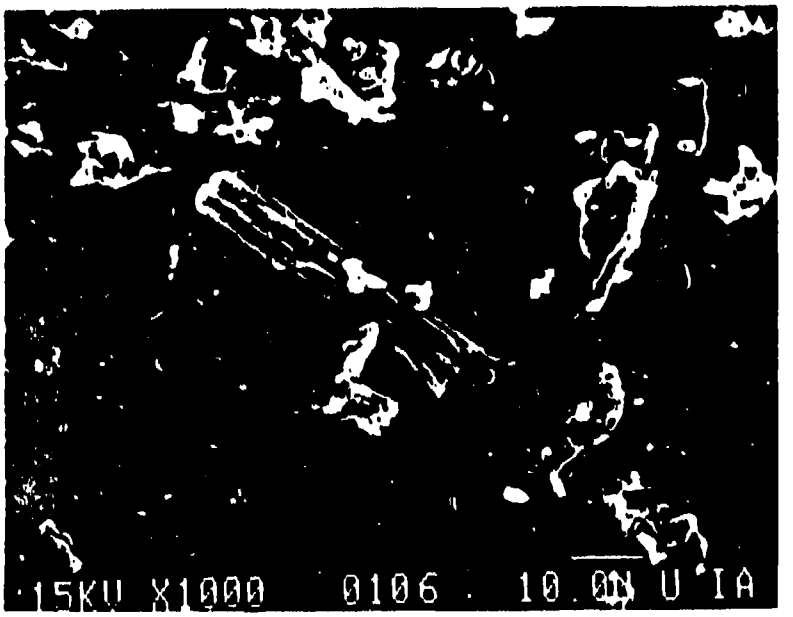
STRUCTURE



A. Solid Properties

1. Color	yellow
2. Odor	none
3. Taste	bitter
4. Appearance	fine powder
5. Scanning Electron Micrographs	

6-Methoxy-8-(6-diethylaminohexylamino) lepidine dihydrochloride



6. Particle Size	Wide distribution with some plate-like crystals as long as 35-50 microns but most falling in the range of 5-10 microns

7. Differential Scanning Calorimetry (DSC)

See attached DSC thermogram (Fig. 1)
M.P. - 187.15°C (10°C/min)
Heat of fusion - 28.38 Cal/gram (11.82 kcal/mole)

8. X-Ray Diffraction

See attached X-ray powder diffraction pattern (Fig. 2)
Below are given the 2θ angles, D values (Å) and relative intensities (I/I') for all diffraction maxima over 2-40°

			"D"	I/I/	
			5.516	100	
			5.660	74	
			5.120	67	
BKG	PEAK	TWO-BETA	"D"		
48	122	5.257	16.811	5	1
48	168	5.382	16.420	7	2
48	1143	5.768	15.334	52	3
68	1314	11.524	7.679	60	4
68	393	12.265	7.216	18	5
68	566	12.5	7.030	25	6
88	622	14.4	6.129	28	7
88	234	14.	5.971	10	8
88	370	15.303	5.790	17	9
88	1458	17.319	5.120		10
88	183	17.479	5.074	8	11
136	483	20.283	4.378	22	12
136	486	20.340	4.366	22	13
136	895	20.841	4.262	41	14
136	401	21.313	4.168	18	15
200	792	22.149	3.9[illegible]	36	16
200	535	22.669	3.922	25	17
200	1619	24.316	3.660		18
200	1432	24.428	3.[illegible]	[illegible]	19
200	[illegible]	25.328	3.[illegible]		20
196	594	26.143	3.409		21
196	813	26.850	3.320		22
196	1090	28.948	3.082	30	23
196	1014	29.382	3.039	49	24
200	540	32.079	2.790	24	25
188	472	36.122	2.487	21	26
188	474	36.169	2.483	21	27

9. Infra-Red Spectrum

Spectrum taken as a KBr pellet dispersion on a Perkin-Elmer IR Model 267 at Medium Scan Speed. See Fig. 3

B. Solution Properties of WR6026·2HCl Lot AF

1. Solubilities

Solvent	Temp (C°)	Solubility (mg/ml)
Water (~pH 2.3)	37°	>200
pH 2 Sulfuric Acid	~25°	>50
pH 6 Phosphate Buffer	~25°	>35
pH 9.4 Borate Buffer	37°	0.088
Absolute Ethanol	~25	>50
Isopropanol	37	12
pH 10.9 (free base)	~37	0.0034
Octanol (free base)	37	~276
Chloroform	~25	>25

2. Dissociation Constants

pK_{a1} = 3.58 ± 0.03
pK_{a2} = 9.79 ± 0.15

3. Partition Coefficient (free base)

Octanol, H_2O (37°C) - 81,120 (log P = 4.91)

4. UV Spectral Data

Solvent	Wavelength (nm)	Molar Absorptivity (ε)
Water	258	20,922
Normal Saline	258	19,913
0.01 N HCl (pH 2) (See Fig. 4)	262	17,548
1/15 M Phosphate Buffer (pH 6)	256	22,260
Isopropanol	264	23,240
Acidified Isopropanol	289	20,251

5. Proton Magnetic Resonance Spectrum
Spectrum taken in D_2O on a Varian Model EM-360 NMR Spectrometer. See Fig. 5.
6. Osmotic Properties
Isotonic concentration = 250 mM (104 mg/ml)

C. Solution Stability of WR6026·2HCl Under Various Conditions

Preliminary studies on the instability of WR6026·2HCl in aqueous solution including spectral changes were reported in Annual Report No. 2 (5). More recently, studies have concentrated on methods by which WR6026·2HCl can be stabilized in solution. A variety of factors have been screened including: pH; type of light; use of a nitrogen purge; use of clear or amber glass container; addition of a chelating agent or one of several antioxidants.

1. Experimental

a. Preparation of Solutions. A liter of pH 2 buffer was prepared by dissolving 3.73 grams of potassium chloride in distilled water along with the addition of 11.8 ml of 1N hydrochloric acid. The pH 6 buffer was prepared by dissolving 8.06 grams of potassium dihydrogen phosphate and 1.32 grams of disodium hydrogen phosphate in enough distilled water to make one liter. The normal saline solution contained 0.9 grams of sodium chloride per liter. The hydroxyethyl cellulose-Tween 80 solution was prepared by stirring a solution containing 10 grams of Tween 80 and 5.0 grams of hydroxyethyl cellulose per liter with a magnetic stirrer until it was clear. Standards of WR6026·2HCl for daily standardization of the liquid chromatograph were prepared by dissolving 150 milligrams of WR6026·2HCl in enough distilled water to make 100 milliliters. Either 2.0, 1.25 or 0.75 milliliters of this stock solution were further diluted with distilled water yielding concentrations of 30, 18.75 or 11.25 micrograms per milliliter respectively.

b. Additives. Tetrasodium ethylenediamine tetraacetic acid was added to either the pH 2 or pH 6 buffer solutions at a concentration of 0.1% (1.0 gram per liter). A variety of antioxidants were screened using the following concentrations in either the pH 2 or pH 6 buffers: 0.01% and 0.1% cysteine hydrochloride; 0.005% thiourea; 0.01% mercapto-1,2-propanediol and 0.13% sodium formaldehyde sulfoxylate.

c. Containers. Either clear glass or amber glass ampules or vials were used.

d. Environmental Conditions. Some of the solutions were purged by bubbling nitrogen for 15 minutes through a glass tube into a 100 milliliter volumetric flask containing the appropriate vehicle. After the purged solution was placed into a vial or ampule the headspace of each was flushed with nitrogen for 30 seconds prior to sealing the container. Other solutions were not purged. Containers were either exposed to normal laboratory florescent light for 8 to 12 hours per day (Temperature range 20-25°C) or to 253.7 nm ultraviolet light in a Rayonet Mini-Photochemical reactor (Temperature 25°C). In the latter case the containers were constantly rotated at 5 RPM past a bank of four lamps at a distance of about one inch. The intensity specification of the 253.7 nm lamp is 1.6×10^4 microwatts per square centimeter 2 inches from the lamp.

e. High Pressure Liquid Chromatographic Assay. The mobile phase consisted of 75% methanol and 25% of a 0.01 M pH 3 phosphate buffer prepared from 0.0088 M sodium dihydrogen phosphate and 0 0012 M phosphoric acid. A five micron Waters cyano-column was used in a Waters Radial Compression Module. A flow rate of 3 milliliters per minute produced a retention time for the peak of interest of about 10 minutes. Injections were made into a 20 microliter loop. A wavelength of 254 nm at a sensitivity of 0.05 absorbance units full scale (AUFs) was utilized for sample analysis. An external standardization method was used with a standard curve prepared each day samples were analyzed.

f. Kinetic Run Procedure. The starting concentration of WR6026·2HCl was always 30 micrograms per milliliter. The several ampules or vials used for each set of conditions were filled with bulk WR6026·2HCl solution. For each time, the contents of one ampule were analyzed in either duplicate or triplicate. In the case of the vials, samples were withdrawn by syringe. All concentrations analyzed at later times were related to the zero time sample which was set at 100%.

C. Results and Discussion

It can be seen that some of the concentrations of WR6026·2HCl remaining after time zero are greater than 100%. This is an artifact based on several factors. Only single ampules were sampled at any one time and there may have been some variation especially in light conditions from ampule to ampule. Even though standard curves were run each day samples were analyzed, a change in chromatographic performance could cause these apparently incongruous results. However, even with

some scatter in the points the differences from one set of conditions to another is great enough so that various conditions can be adequately screened.

The stability of WR6026·2HCl in a hydroxyethyl cellulose (HEC)/Tween 80 mixture and in a normal saline solution was determined because these are standard vehicles for the drug in animal study work carried out at Walter Reed. It can be seen from the data in Table I that the solutions are best stored in amber glass containers and should be freshly prepared on at least a weekly basis.

The data in Table II demonstrates the greater instability of WR6026·2HCl at pH 6 compared to pH 2 particularly when the Rayonet Mini-Photochemical Reactor is used as the ultraviolet light source.

Table I. Stability of WR6026·2HCl in Saline Solution or an Aqueous Hydroxyethyl Cellulose/Tween 80 Mixture Exposed to Room Light

	Conditions			
	HEC/Tween		Saline	
	Clear Glass	Amber Glass	Clear Glass	Amber Glass
Time (hrs)	Percentage Remaining			
0	100	100	100	100
168	70	91	85	109
288	67	84	14	99
480	78	81	-	77
576	71	90	-	90
1008	66	58	-	42

Table II. Stability of WR6026·2HCl in Aqueous Solution in Clear Glass.

	Conditions			
	pH 2		pH 6	
	Room Light	UV Light	Room Light	UV Light
Time (hrs)	Percentage Remaining			
0	100	100	100	100
48	-	-	-	50
72	93	90	93	4
96	-	89	-	0
144	74	68	77	-
168	72	83	67	-
216	23	-	40	-
240	-	71	-	-
264	-	59	-	-

The enhancement of WR6026·2HCl stability in amber glass is clearly shown in Table III. The difference between clear and amber glass containers is somewhat more apparent at pH 6 than at pH 2.

Table III. Stability of WR6026·2HCl in Nitrogen Purged Aqueous Solutions Exposed to Ultraviolet Light (253.7 nm).

	Conditions			
	pH 2		pH 6	
	Clear Glass	Amber Glass	Clear Glass	Amber Glass
Time (hrs)	Percentage Remaining			
0	100	100	100	100
24	100	91	95	85
48	-	92	78	93
72	-	94	52	84
96	87	92	71	92
120	80	-	-	-
144	85	-	-	-
168	79	89	-	87
240	-	92	-	84

The effect of purging the solution with nitrogen before sealing the ampules is shown in Table IV. Again at pH 2 where WR6026·2HCl already appears to be more stable, the usefulness of a nitrogen purge is doubtful. Through the first week there is little difference indicating the added effort of purging with nitrogen is not warranted.

Table IV. Stability of WR6026·2HCl in Aqueous Solutions in Clear Glass Ampules Exposed to Ultraviolet Light (253.7 nm).

	Conditions			
	pH 2		pH 6	
	No Nitrogen Purge	Nitrogen Purge	No Nitrogen Purge	Nitrogen Purge
Time (hrs)	Percentage Remaining			
0	100	100	100	100
24	-	100	-	95
48	-	-	50	78
72	90	-	4	52
96	89	87	0	71
120	-	80	-	-
144	68	85	-	-
168	83	79	-	-
240	71	-	-	-
264	59	-	-	-

Since heavy metals frequently catalyze photochemical or oxidation reactions, ethylenediamine tetraacetic acid (EDTA) was used as a chelating agent to further reduce their concentration in the solution. It can be seen in Table V that in clear glass containers at pH 2 the EDTA for some unknown reason actually seems to decrease the stability of WR6026·2HCl and at pH 6 there is little difference. The same study carried out in amber glass ampules shows in Table VI that the addition of EDTA does little to enhance the stability of WR6026·2HCl. Consequently, its addition to the system is not recommended.

Table V. Stability of WR6026·2HCl in Nitrogen Purged Aqueous Solution in Clear Glass Ampules Exposed to Ultraviolet Light (253.7 nm).

	Conditions			
	pH 2		pH 6	
	No EDTA	0.1% EDTA	No EDTA	0.1% EDTA
Time (hrs)	Percentage Remaining			
0	100	100	100	100
24	100	-	95	92
48	-	59	78	77
72	-	42	52	53
96	87	39	71	77
120	80	0	-	-
144	85	-	-	-
168	79	-	-	-

Table VI. Stability of WR6026·2HCl in Nitrogen Purged Aqueous Solution in Amber Glass Ampules Exposed to Ultraviolet Light (253.7 nm).

	Conditions			
	pH 2		pH 6	
	No EDTA	0.1% EDTA	No EDTA	0.1% EDTA
Time (hrs)	Percentage Remaining			
0	100	100	100	100
24	91	92	85	85
48	92	95	93	88
72	94	93	84	92
96	92	91	92	92
168	89	91	87	83
240	92	90	84	49

Table VII. Stability of WR6026·2HCl in pH 2 Antioxidant Solutions in Clear Glass Exposed to Ultraviolet Light (253.7 nm).

	Conditions				
	No Anti-oxidant	.01% Cysteine HCl	0.1% Cysteine HCl	.005% Thiourea	.01% Mercapto-1,2-propanediol
Time (hrs)	Percentage Remaining				
0	100	100	100	100	100
24	-	96	95	95	95
48	-	90	88	-	-
72	90	85	86	79	84
96	89	84	82	75	79
144	68	74	68	64	-
168	83	65	-	55	-
192	-	-	-	-	-
240	71	-	-	46	54
264	59	-	-	-	-

Table VIII. Stability of WR6026·2HCl in pH 2 Cysteine HCl Solution Exposed to Ultraviolet Light (253.7 nm).

	Conditions			
	.01% Cysteine HCl		0.1% Cysteine HCl	
	Clear Glass	Amber Glass	Clear Glass	Amber Glass
Time (hrs)	Percentage Remaining			
0	100	100	100	100
24	96	108	95	110
48	90	-	88	-
72	85	105	86	114
96	84	107	82	106
144	74	-	68	-
168	65	-	-	-
192	-	105	-	104
240	-	94	-	100
264	-	94	-	94

Several antioxidants were tested using the severe conditions of clear glass and ultraviolet light at 253.7 nm as shown in Table VII. It can be seen that there appears to be only small differences between using an antioxidant and not using one with this set of conditions. Table VIII compares the results of two concentrations of cysteine hydrochloride in both clear and amber glass. It appears that there is little difference between the 0.01% and 0.1% cysteine hydrochloride solutions.

The stabilizing effect of amber glass is again readily observed and is probably more important than the presence of any antioxidant. The data in Table IX again demonstrates the effect of amber glass in the thiourea solutions. A more realistic set of conditions is shown in Table X where under the effect of room light it is apparent that the solution containing the 0.01% cysteine hydrochloride is much more effective in preventing the breakdown of WR6026·2HCl than either no antioxidant or the 0.1% mercapto-1,2-propandiol.

Table IX. Stability of WR6026·2HCl in a pH 2 Solution of 0.005% Thiourea Exposed to Ultraviolet Light (253.7 nm).

	Conditions	
	Clear Glass	Amber Glass
Time (hrs)	Percentage Remaining	
0	100	100
24	95	95
48	-	103
72	79	-
96	75	111
120	-	81
144	64	-
168	55	98
216	-	100
240	46	-

Table X. Stability of WR6026·2HCl in pH 2 Antioxidant Solutions in Clear Glass Ampules Exposed to Room Light.

	Conditions		
	No Antioxidant	0.01% Cysteine HCl	0.1% Mercapto-1,2-propanediol
Time (hrs)	Percentage Remaining		
0	100	100	100
24	-	-	93
72	93	-	-
96	-	97	79
120	-	-	74
144	74	-	-
168	72	-	77
192	-	100	53
216	23	-	-
264	-	-	33
288	-	97	-
432	-	97	-
504	-	95	-
600	-	99	-

The results for the use of sodium formaldehyde sulfoxylate as an antioxidant are not reported since the time zero sample was devoid of any WR6026·2HCl. This apparent adverse effect of this combination will not be examined any further.

3. Conclusions

1. The drug is most stable at pH 2, with 0.01% cysteine as an antioxidant in amber glass. A study of 0.01% cysteine at pH2 in clear glass indicated that there was no significant degradation in room light after 25 days (the duration of the study).

2. Using a N_2 headspace does not improve drug stability.

3. Using EDTA does not improve drug stability.

4. 0.01% cysteine was the most effective antioxidant screened.

5. Solutions of the drug in HEC/Tween and normal saline were found to not be stable in room light and room temperature for very long, but stability was markedly improved in amber glass containers.

D. REFERENCES

1. Lach, J.L., et al., Annual Report No. 2, July 1981, Contract No. DAMD 17-79-C-9136, College of Pharmacy, University of Iowa, Iowa City, Iowa.

E. APPENDIX OF PHYSICOCHEMICAL DATA

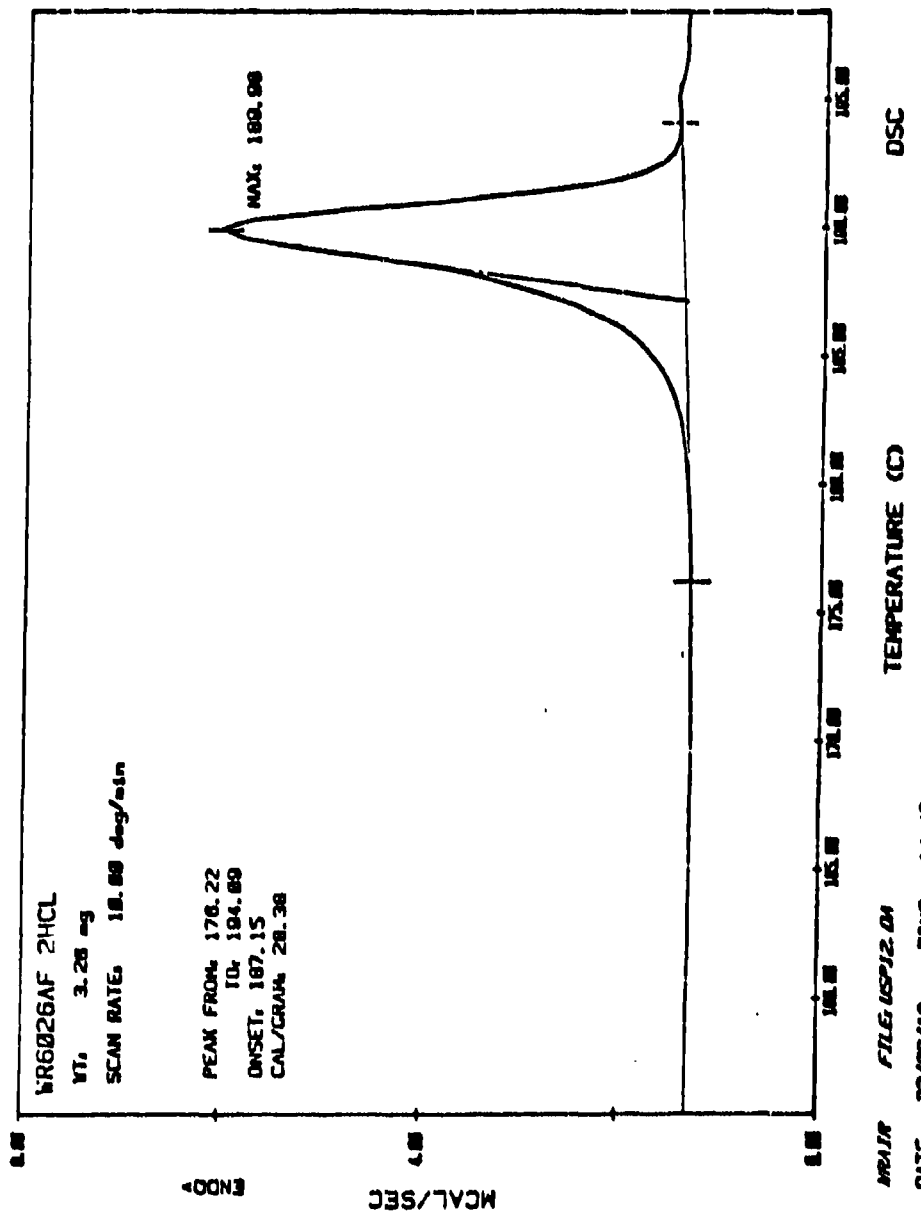


Figure 1: DSC Thermogram of WR6026·2HCl Batch AF

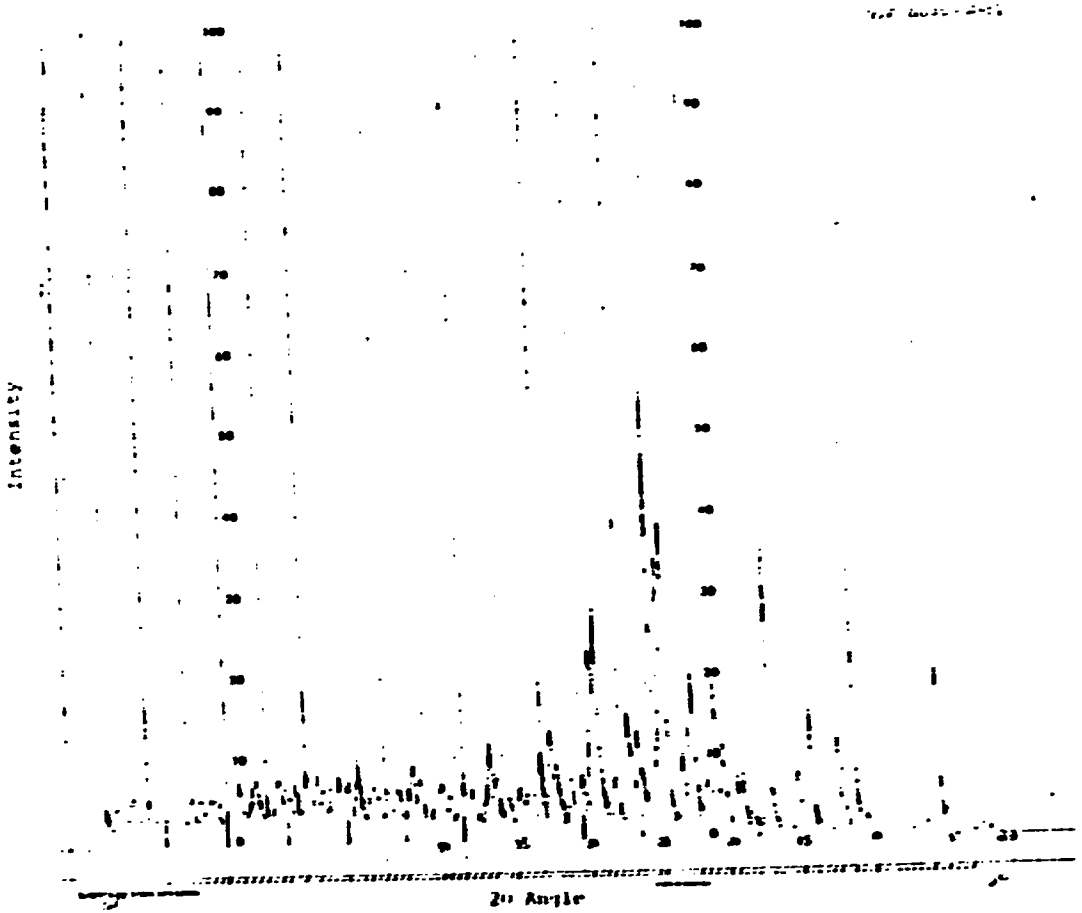


Figure 1: X-ray powder diffraction pattern for [illegible] Batch AF

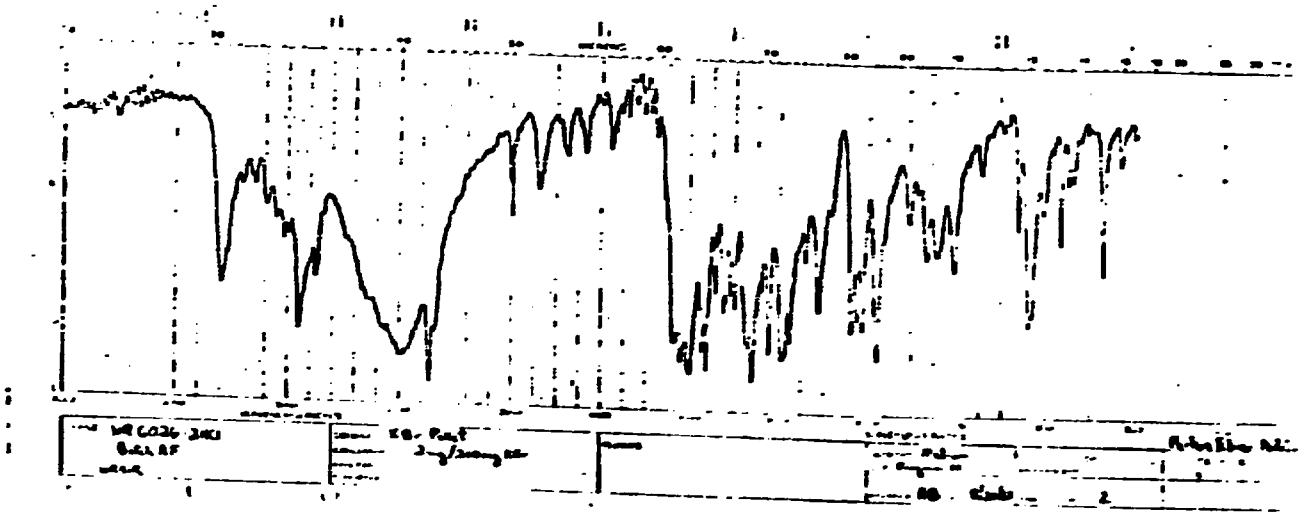


Figure 3: IR Spectrum of WR6026-2HCl Batch AF (KBr Pellet)

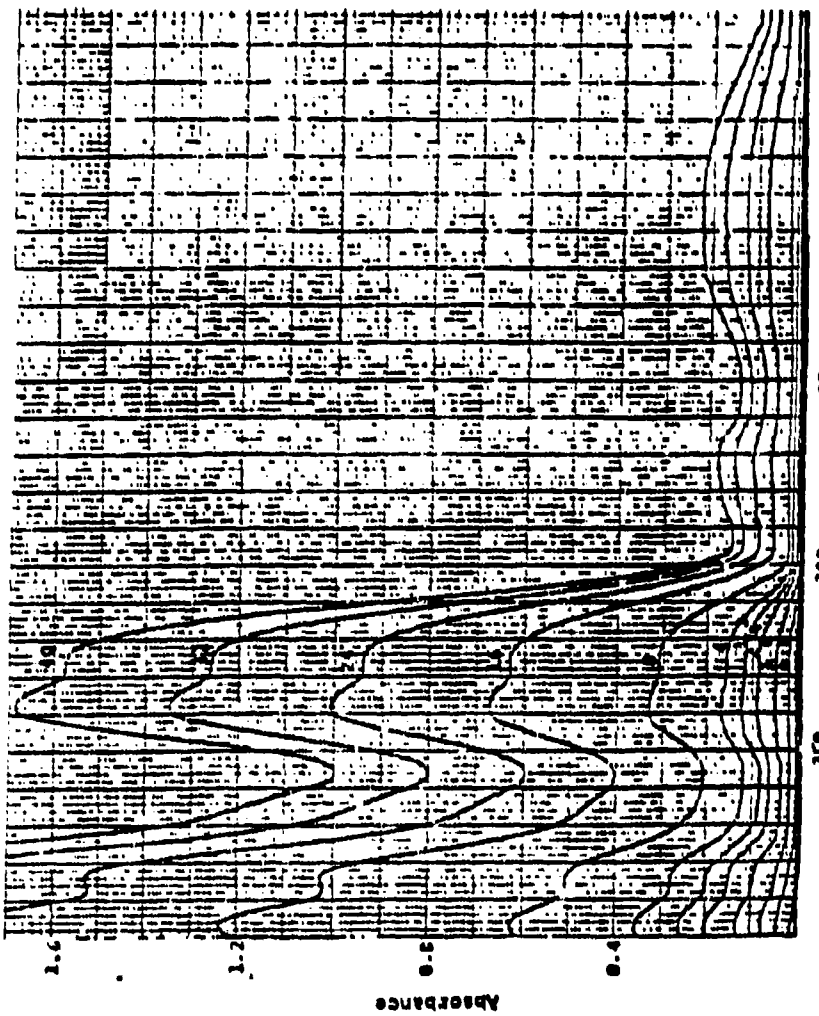


Figure 4. UV Spectrum of WR6026-2HCl in 0.01 N HCl (pH 2) (concentrations are micrograms/ml) Batch AF

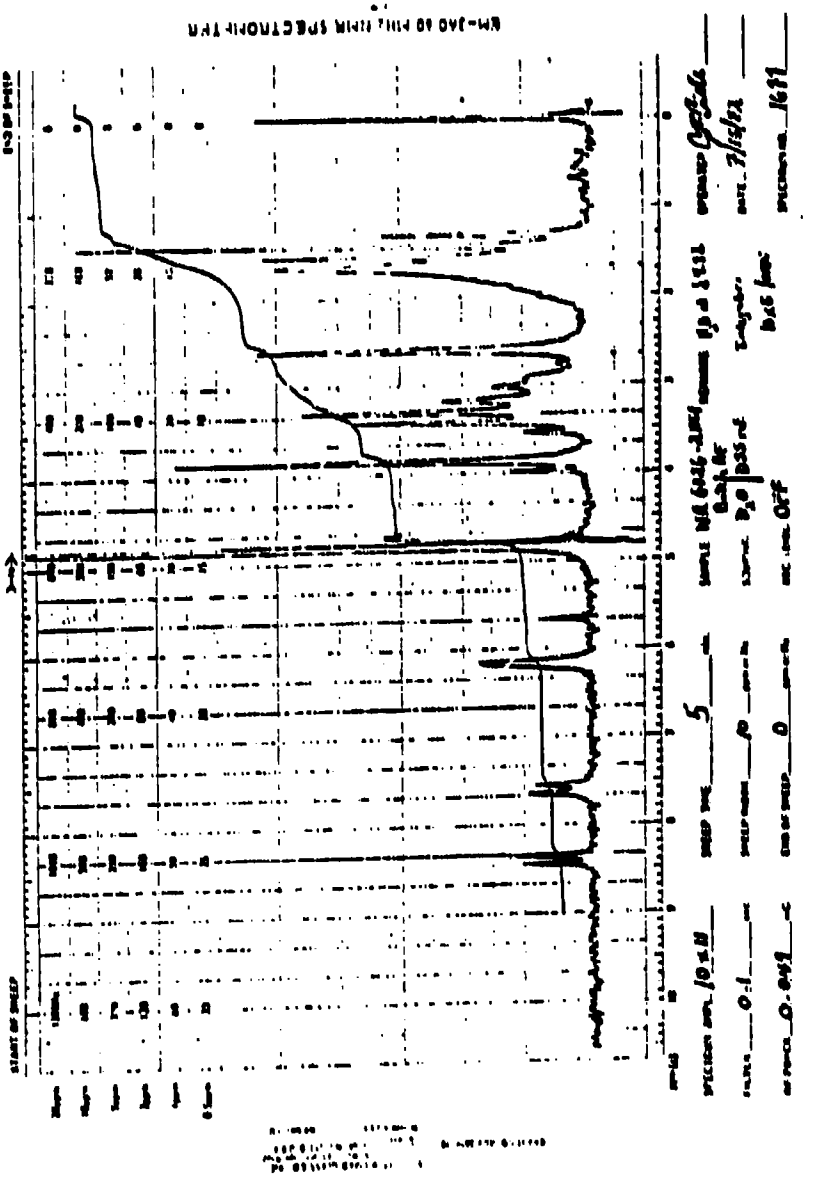


Figure 5: NMR Spectrum of WR6026-2HCl Batch AF in D_2O.

AD _____

Quarterly Report Number 13

Formulation and Production of WR638 (Lot AV) 250 MG (Anhydrous Equivalent Capsules (WRA-09-10182)

John L. Lach
Douglas R. Flanagan
Lloyd E. Matheson, Jr.

January, 1983

Supported by

U.S. Army Medical Research and
Development Command
Fort Detrick
Frederick, Maryland 21701-5012

Contract No. DAMD17-79-C-9136

College of Pharmacy
University of Iowa
Iowa City, Iowa 52242

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Resume' of Progress

Effort is continuing on the development of a liposomal delivery system for WR6026·2HCl. Work during this period is centered on sizing liposomes by flow cytometry and freeze-fracture electron microscopy. Other work has been concerned with confirmation of entrapment efficiency using radiolabelled WR6026·2HCl.

The dissolution and solubility properties of WR171,669·HCl are being evaluated further to rationalize the poor bioavailability of this compound. Improvements in the dissolution test methodology are being made to make the test less cumbersome and more reflective of *in vivo* performance of WR171,669·HCl dosage forms. The solubility has been investigated in a number of solvents and in various pH media to obtain solvent conditions which would permit use of a lower volume of fluid for the dissolution test.

Objective

The objective of this work is to formulate and produce capsules of WR638 (Lot AV) containing 250 mg of anhydrous drug for use in human clinical trials.

Summary

Capsules containing the equivalent of 250 mg of WR638 were formulated and produced. The formulation incorporates WR638 and anhydrous lactose encapsulated into #00 clear gelatin capsule shells.

The weight variation test for twenty capsules (Lot WRA-09-10182) showed an average fill of 630.9 mg per capsule with a range from 582.2 to 691.7 mg. The balance was tared with an empty capsule shell.

The content uniformity of ten capsules yielded an average of 102.9% of label claim with a range of 99.4 to 110%.

No disintegration test was carried out since the contents of the capsule is emptied prior to administration into an appropriate vehicle.

USP requirements for weight variation and content uniformity were met.

Methodology

The sample of WR638 (Lot AV) was received on October 18, 1982 and was recorded in raw material receiving notebook number 17. The drug was assigned material lot number 726-017-726 and control number GG-102-010. The drug was stored in the original amber glass container in the refrigerator until use.

Purity

The purity of the drug was determined using the iodometric procedure described by Lim (1). Water content was determined using the Karl Fischer titration method.

Formulation Ingredients

An identification test was carried out on the formulation excipient (i.e., anhydrous lactose, USP) according to compendial requirements. WR638 (Lot AV) was identified by its infrared spectrum run in Nujol. A certificate of analysis from the manufacturer for the anhydrous lactose is included in Appendix I, p. I-11.

Manufacturing Procedure

The WR638 was milled through a 40 mesh screen on a small Fitzpatrick mill. After milling, 1.69 kg of WR638 was placed in an 8 quart V-blender shell along with 1.31 kg of anhydrous lactose. This mixture was blended for 15 minutes. Number 00 clear gelatin capsules were filled with 640 mg of powder blend using a Deltay Manual Capsule Filling machine. Procedures are described in detail in Apendix I, p. I-3.

USP Methods and Requirements

The weight variation test for capsules is described in USP XX (1). Twenty capsules must be weighed individually and the individual weights must be within the limits of 90 to 110% of the average weight. This test was conducted on the capsules using a Mettler H51 AR semimicro balance.

The content uniformity test for capsules is described in USP XX (2). Ten capsules were assayed individually using an iodometric titration method. The content of each of not less than nine capsules was required to be within the limits of 85 to 115% of the label claim.

No dissolution test was performed on the capsules because of the high solubility of WR638. Compendial dissolution tests are required for drugs or drug formulations which have poor solubility which could result in poor dissolution characteristics.

Results

Disintegration Test

This test was not performed since the capsule contents are emptied into an appropriate vehicle before administration.

Weight Variation Test

The weight variation test for twenty capsules produced an average fill of 630.9 mg per capsule with a fill range of 582.2 to 691.7 mg. The acceptable fill range is 576 to 704 mg.

Content Uniformity Test

The content uniformity of the capsule formulation yielded an average of 102.9% of label claim with a range of 99.4 to 110%.

Batch Size

The theoretical number of capsules to be filled in Lot WRA-09-10182 was 4844 capsules. The actual number filled after manufacturing losses was 4695.

Packaging

Twenty-five capsules were placed into two ounce glass amber prescription squares. The void space was filled with Rayon Pharmaceutical coil.

Labels

The label was prepared as per instructions and is shown on p. I-2 of Appendix I.

Conclusions

The capsule formulation of WR638 met all compendial requirements.

References

1. The United States Pharmacopeia, XX, 989 (1980).

2. Ibid., p. 956.

Appendix I

Manufacturing Formula and Quality Control Tests on WR638 Capsules (250 mg anhydrous equivalent).

Form CP 1
1507

University of Iowa College of Pharmacy
MANUFACTURING FORMULA

Page 1 of ______ pages

Product: WR638·Na, 250 mg capsules (anhydrous equivalent)	List No. 9997
Formula Written by [illegible] Date 10/18/82 Formula Checked by [illegible] Date 10/18/82	Batch Size 4844 capsules
Production authorized by [illegible]	Control No. WRA-09-10182

Analysis

Assay for	Theoretical	Actual
WR638·Na	250 mg anhydrous	257.3 mg anhydrous

Control Assay No. A-063 Worksheet Checked by J. F. S[illegible] Date 11-10-82

Specifications

	Initial	Theoretical	Actual
Size	KM	#00 Gelatin capsules	[illegible]
Weight	KM	640 mg/capsule	630.[illegible] mg/capsule
Color	KM	clear cap/body	clear cap/body
Disintegration			
Tablet Hardness			
Tablet Thickness			
Clarity			
pH			
Density			
Viscosity			
Sedimentation			
Gross Appearance			
Sterility			
Pyrogens			
Other: Weight Variation	KM	Meet USP Specifications	Passed

Package and Label

Type of Container: Amber glass Rx vials

Size of Container: 2 ounce

Method of Packaging

Machine count capsules

Remarks

Void space in vial filled with [illegible] cotton coil.

WALTER REED INSTITUTE OF RESEARCH
[illegible]

[illegible] 11/[illegible]

Page _ of _

Product WR6038:Na, 2.. ..oules (anhydrous equivalent) Lot No. 9997

Batch Size 6844 capsules Control No. WRA-09-10182

Caution or Special Instructions

1507

EACH CONTAINS	INGREDIENTS AND DIRECTIONS	RAW MAT'L CONTROL NO.	INITIAL	AMOUNT PER BATCH
	Prior to blending to make the capsule formulation the WR6038:Na was milled in a small Fitzpatrick mill using a 40 mesh screen.		[illegible]	
	Add to a 8 qt. plastic V-blender shell:			
	WR6038:Na Source: Walter Reed Army Institute of Research Lot No.: AV Material Lot: 774-017-736 Exp. Date: 10-18-84	RC 102-010	[illegible]	1.64 kg
	Lactose, USP, Anhydrous Mfr.: Sheffield Mfr. Lot: INFO9 Material Lot: 819-016-814 Exp. Date: 7-1-83	AA-071-007	[illegible]	1.31 kg
	Blend for 15 minutes: Blending Start: 7:15 Blending Stop: 7:30		[illegible]	
	Weight of final blend 2.99 kg		[illegible]	
	Remove a sample for assay and a sample for retention.		[illegible]	
	The fill of the capsule is determined from in-process assay.			
	In-process analysis of powder blend using iodometric assay. 239.0 mg anhydrous drug per 575 mg blend 247.7 mg anhydrous drug per 575 mg blend Average: 243.9 mg/575 mg 243.9 / 250 = 97.6% of label/fill X = 97.6% of label/fill		[illegible]	

Page ___ of ___ Page

...bject ___VK638-Na, 250 mg. capsules (anhydrous equivalent) List No. ___ ,9947 ...

...ch Size ___4844 capsules. ___ Control No. WRA-09-J0182 ...

...ution or Special Instructions

507

...TE OR PAIN.	INGREDIENTS AND DIRECTIONS	RAW MAT'L CONTROL NO.	INITIAL	ANALYSIS PER BATCH
	Fill 340 mg. of powder blend into 100 gelatin capsules, clear body/cap. Mfrd. Sherer Mfr. Lot: PIA-0171-IN-728-1 Material Lot: 309-017-169 Exp. Date: 9-1-84			
	Fill capsules 37 at a time, using the Dolley capsule filling machine (manual).			
	Add 26.5 gm of powder blend for each set of 37 capsules.			
	In-process fill weights of 10 capsules:			
	1. 6.48 2. 6.48 3. 6.48 4. 6.48 5. 6.48 6. 6.48 7. 6.51 8. 6.47 9. 6.48 10. 6.48 11. 6.48 12. 6.41 13. 6.47 14. 6.48 15. 6.48 16. 6.48 17. 6.48 18. 6.48 19. 6.48 20. 6.48 21. 6.48 22. 6.48 23. 6.48 24. 6.48 25. 6.41 26. 6.48 27. 6.48 28. 6.48 29. 6.48 30. 6.48 31. 6.48 32. 6.48 33. 6.48 34. 6.48 35. 6.41 36. 6.48 37. 6.48 38. 6.48 39. 6.48 40. 6.48 41. 6.48 42. 6.48 43. 6.48 44. 6.48 45. 6.48 46. 6.48 47. 6.48 48. 6.48 49. 6.48 50. 6.48 51. 6.48 52. 6.48 53. 6.48 54. 6.48 55. 6.48 56. 6.48 57. 6.48 58. 6.48 59. 6.48 60. 6.48 61. 6.48 62. 6.48 63. 6.48 64. 6.48 65. 6.48 66. 6.48 67. 6.48 68. 6.48 69. 6.48 70. 6.48 71. 6.48 72. 6.48 73. 6.48 74. 6.48 75. 6.48 76. 6.48 77. 6.48 78. 6.48 79. 6.48 80. 6.48 81. 6.48 82. 6.48 83. 6.48 84. 6.48 85. 6.48 86. 6.48 87. 6.48 88. 6.48			

(6.48)(82) = 4679

4675

-40

4635

Page ___ of ___ Pages

Product Ampicillin, 250 mg capsules Lot No. [illegible]

Batch Size 4864 capsules Control No. AMA 09-1018

Caution or Special Instructions

1507

THIS CONTAINS	INGREDIENTS AND DIRECTIONS	RAW MATL. LOT NO.	INITIAL	AMT. OF PER PACK
	40 capsules, [illegible] for quality control			
	Capsules, [illegible] per bottle			
	Label [illegible]			
	2 oz. amber Rx squibbs, Commonwealth Material Lot: M-609-017-609	PP-AMC 011	JM	
	Void space filled with: Bayou Pharmaceutical Cotl. Kendall Co. Mix. Lot No.: FM 1081 Mat. Lot No.: M-184-017-274	CP-010-006	JM	
	124 bottles filled.			
	Retained samples 49 capsules.		JM	

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Iowa City Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4520

PURITY DETERMINATIONS

Product: WR638-Na, 250 mg capsules (anhydrous equivalent)

Lot No.: WRA-09-10182

Water Content by Karl Fischer Titration

26.97%
27.24%
28.45%
26.99%

Average: **27.41% ± 0.7%**

Purity by Iodometric Procedure

72.47% (expressed as anhydr us drug)

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IN-PROCESS ANALYSIS OF POWDER BLEND

Product: WR638-Na, 250 mg capsules, (anhydrous equivalent)

Lot No.: WRA-09-10182

Method: Iodometric Titration

222.8 mg anhydrous drug/575 mg blend
226.98 mg anhydrous drug/575 mg blend

Average = 224.9 mg anhydrous drug/575 mg blend

MS-2, p. 21

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Department of Pharmaceutical Service

(310) 353-4520

WEIGHT VARIATION OF FINISHED CAPSULES

Product: WR638-Na, 250 mg capsules, (anhydrous equivalent)

Lot No.: WRA-09-10182

No.	mg/capsule	No.	mg/capsule
1	619.6	11	609.3
2	609.9	12	639.8
3	582.2	13	626.6
4	609.2	14	651.5
5	612.2	15	639.2
6	628.6	16	691.7
7	640.4	17	644.5
8	619.9	18	644.5
9	656.7	19	641.7
10	615.2	20	630.9

Average Fill: 630.91 mg/capsule

Deviation from low (582.2) = 7.72%
Deviation from high (691.7) = 9.63%

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CONTENT UNIFORMITY OF FINISHED PRODUCT

Product: WR638 Na, 250 mg capsules (anhydrous equivalent)

Lot No.: WRA-09-10182

No.	mg/capsule	% of label
1	274.9	109.96
2	248.5	99.40
3	255.9	102.36
4	259.1	103.64
5	249.6	99.84
6	259.1	103.64
7	260.1	104.04
8	248.5	99.40
9	249.6	99.84
10	267.5	107.00

Lactose, USP, Anhydrous, Sheffield Lot No. 1NF09, PS # 819-016-819

Identification Test: **Passed**
AA-071-007
(Certificate of analysis attached)

Pharmaceutical Services
College of Pharmacy
The University of Iowa
Iowa City, Iowa 52242

SHEFFIELD PRODUCTS — PROTOCOL OF MEMV

819-016-819

CUSTOMER UNIVERSITY OF IOWA
[illegible] PURCHASING DEPT
IOWA CITY IOWA 52242

ATTN PURCHASING

PRODUCT LACTOSE U.S.P. ANHYDROUS DIRECT TABLETING

LOT NO. INF09 — DATE SHIPPED 6-24-81
CUSTOMER ORDER NO [illegible] V-C 371 — NUMBER OF DRUMS 3
INVOICE NO 12498

RESULTS OF ASSAY WHERE APPLICABLE TO PRODUCT SHIPPED:

CHEMICAL/PHYSICAL		MICROBIOLOGICAL	
SOLUBILITY	PASS	STAND. PLATE COUNT	<100/GRAM
MOISTURE %	0.54 - 0.54	THERMOPHILE COUNT	
ASH %	0.052	COLIFORM	NEGATIVE
HEAVY METALS	<5 PPM	SALMONELLA	NEGATIVE
SPECIFIC ROTATION	55.05	MOLD	<50/GRAM
ACIDITY	PASS		
5% (10) SOL 3	4.1 - 4.8		
METHANOL SOL. RESIDUE	0.02		

This copy for your files

RECEIVED
JUN 29 1981
[illegible] DEPT

DATE 6/24/1981

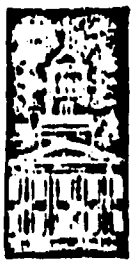
SHEFFIELD PRODUCTS, BOX 398, MEMPHIS, TENN. 38101 — KRAFT INC

[illegible]

The University of Iowa
Iowa City Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4520



APPROVAL FOR SHIPMENT FORM

Product Name: WR638-Na 250 mg capsules, lot WRA-09-10182

Container Size: 25 caps. Dosage Form: capsule

Acceptable Container: 182 Rejects: 0

Total Units Shipped: 182

Date Shipped: November 1, 1982

Delivery Ticket Number: _____

Name and Address of Receiver:

Dr. Larry Fleckenstein
Forest Glen Annex
Building 500
Brookville Road
Walter Reed Army Institute of Research
Silver Springs, MD 20910

Approval of Shipment by: Rlyd E. Mathers Jr.

Pharmaceutical Services
College of Pharmacy

University of Iowa
Iowa City, Iowa

PRODUCT RELEASE FORM — Part A

Product: WR638·Na, 250 mg capsule

Lot No.: WRA-09-10182

Batch Size: 4844 capsules

Date Received by Warehouse: 10/18/82

Quantity	Size
184 bottles of 25 capsules each plus	
partial bottle of 19	

Warehouse: Place this product in quarantine. Please match this form with the release form before placing the product in use.

Part A remains with product until released.

(Detach along dotted line)

PRODUCT RELEASE FORM — Part B

Part B remains with Quality Control Department Analysis Sheets

Product: WR638·Na, 250 mg capsule

Lot No.: WRA-09-10182

Batch Size: 4844 capsules

Warehouse: Please (release) ~~destroy, return to mfg.~~) this product and remove from quarantine.

Signature: Ing-Jong Chi

Date Released: 10-29-82

AD _____

Quarterly Report Number 14

Formulation and Production of 250 Mg WR180,409·H_3PO_4 (Lot AD) Tablets (WRA-10-02283) and Matching Placebos (WRA-11-02283)

John L. Lach
Douglas R. Flanagan
Lloyd E. Matheson, Jr.

April, 1983

Supported by

U.S. Army Medical Research and
Development Command
Fort Detrick
Frederick, Maryland 21701-5012

Contract No. DAMD17-79-C-9136

College of Pharmacy
University of Iowa
Iowa City, Iowa 52242

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Resume' of Progress

1. There is continuing effort on the development of the WR6026·2HCl liposome drug delivery system. Special attention was given to the reproducibility of the assay and aliquot withdrawal for administration. Such reproducibility studies are in preparation for further animal trials of liposome entrapped WR6026. These trials may require removal of unentrapped drug at the time of administration, hence requiring studies to determine how reproducibility the aliquots can be withdrawn from a liposome batch, washed and assayed for content.

2. Polyvinylpyrolidone (PVP) coprecipitates of radiolabelled WR171,669·HCl were prepared for oral absorption studies in dogs. Since the PVP coprecipitates of this compound have dissolution rates much higher than pure drug, it was deemed valuable to determine whether the in vitro dissolution difference would be reflected in in vivo bioavailability differences. To this end, capsules of PVP coprecipitates of ^{14}C-WR171669·HCl were prepared and sent to WRAIR for evaluation.

Objective

The objective of this work is to formulate and produce coated 250 mg and identical placebo tablets of WR180,490·H_3PO_4 (lot AD) for use in human clinical trials.

Summary

Tablets containing the equivalent of 250 mg of WR180, 409·H_3PO_4 and matching placebos were formulated.

The weight variation test for twenty uncoated tablets containing active ingredient (Lot WRA-10-02282) showed an average weight of 513.6 mg per tablet with a range from 496 to 527 mg. The weight variation test for twenty uncoated placebo tablets (Lot WR-11-02283) showed an average weight of 523 mg per tablet with a range from 506 to 549 mg. USP requirements were met.

The content uniformity of ten individual uncoated tablets produced an average of 245.6 mg of WR180,409·H_3PO_4 per tablet (98.2% of label claim) with a range from 228.0 mg (91.2% of label claim) to 251.5 mg (100.6% of label claim). UPS requirements were met.

Disintegration tests carried out on the coated active and coated placebo tablets yielded disintegration times of 2.45 and 2.55 minutes respectively for six tablets.

Dissolution testing carried out on six coated active tablets showed the average percentage of drug dissolved in ten minutes was 90.6% (range 82.9 - 95.2%) and in 70 minutes the average percentage dissolved was 99.1% (range 96.6 - 100.7%).

Methodology

The sample of WR180,409·H_3PO_4 (Lot AD) was received on 9 Feb., 1983 and was recorded in raw materials receiving notebook number 17. The drug was assigned material lot numbers 960-071-960 and control number HH-023-096. The drug was stored in the original amber glass containers in the refrigerator until use.

Purity

The purity of the drug was taken as 99.1%.

Formulation Ingredients

The WR180,409·H_3PO_4, Lot AD, was identified by matching both infrared and ultraviolet spectra. Identification tests on the formulation ingredients were carried out according to compendial requirements where possible and are reported in Appendices I, II and III. In the case of Amberlite IRP-88, potassium was identified. For the methylene chloride, the specific gravity was determined. Certificates of analysis are present in the batch records. All materials were correct.

Manufacturing Procedure

The 250 mg formulation (WRA-10-02283) was produced by mixing 580.2 gm of WR180,409·H_3PO_4 (Lot AD); 201.25 gm of Avicel PH 101, NF; 172.5 gm of hydrous lactose, USP; and 5.75 gm of magnesium stearate, NF in an 8 quart V-blender for two minutes. This blend was then slugged using a Colton 4-station tablet machine. After breaking the slugs, the blend was passed through a 20 mesh screen and transferred to the 8 quart V-blender. At this point an additional 201.25 gm of Avicel PH 101 was added along with 23 gm of Amberlite IRP88, NF; and 2.88 gm of magnesium stearate. The mixture was blended for two minutes and an additional 2.88 gm of magnesium stearate was added. Blending again continued for two minutes. The tablets were punched using 7/16 inch deep concave punches on the Colton 4-Station tablet machine. Procedures are described in detail in Appendix I, p. I-2.

The matching placebo tablets (WRA-11-02283) were produced by mixing 7.0 kg of microcrystalline cellulose, NF (Avicel PH 101); 3.0 kg of hydrous lactose, USP; 200 gm of Amberlite IRP-88, NF; and 50 gm of magnesium stearate in a 3 cubic foot stainless steel V-blender for two minutes. An additional 50 gm of magnesium stearate was then added and blending continued for another two minutes. The tablets were punched using 7/16 inch punches on the Colton 4-Station tablet machine. Procedures are described in detail in Appendix II, p. II-2.

Both the active and placebo batches were coated green.

The solvent system for the solvent film coating solution consisted of 8.0 kg of methylene chloride and 4.16 kg of absolute alcohol, USP in a stainless steel container. To the solvents 338 gm of hydroxypropyl methylcellulose, 15 cps, NF; 79 gm of ethylcellulose, 10 cps, NF; and 52 gm of triacetin, food grade was added and mixed for 10 minutes. The container was then tightly closed and allowed to set for two hours before use. The green Colorcon color concentrate suspension (Formula K-1-3335-A) was mixed with a high speed mixer for 15 minutes and 377 gm was added with mixing to the previously prepared polymer solution.

The active and placebo tablets were film coated using a Freund Model [illegible]-48 Hi-Coater. The temperature-time curves for the spray process are included in Appendix III.

USP Methods and Requirements

The weight variation test for tablets is described in USP XX (1). Twenty tablets must be individually weighed and the individual weights of not more than two tablets can differ from the average weight by not more than 5% for tablets weighing more than 324 mg. No single tablet can differ by more than 10%. This test was conducted on uncoated active and placebo tablets using a Mettler H51AR semimicro balance according to the USP XX requirements.

The content uniformity test for tablets is described in USP XX (1). Ten tablets analyzed individually must have contents within the limits of 85.0 to 115.0 percent. A UV spectrophotometric assay was utilized.

The disintegration test for tablets is described in USP XX (1). Six coated tablets from both the active and placebo lots were tested using 900 cc of distilled water at 37°C as the medium.

The dissolution test for tablets is described in USP XX (1). Six coated tablets (WRA-10-02283) were tested using dissolution apparatus number one, 1000 ml of 0.1 N HCl, a temperature of 37°C and a rotational speed of 100 rpm. Due to interference with the WR180,409 assay from the green film coating a high pressure liquid chromatographic assay was developed and used. The assay used: a Hamilton PRP-1 column; a mobile phase consisting of 75% methanol/25% of a 1% phosphoric acid solution; flow rate, 1.5 ml/minute; a 20 µl loop injector and a UV detector at 254 nm.

Results

Weight Variation Test

The weight variation test for twenty uncoated tablets containing active ingredient (Lot WRA-10-02283) showed an average weight of 513.6 mg per tablet with a range from 496 to 527 mg. The weight variation test for twenty uncoated placebo tablets (Lot WRA-11-02283) showed an average weight of 523 mg per tablet with a range from 506 to 549 mg.

Content Uniformity Test

The content uniformity of ten individual uncoated tablets produced an average of 245.6 mg of WR180,409·H_3PO_4 per tablet (98.2% of label claim) with a range from 228.0 mg (91.2% of label claim) to 251.5 mg (100.6% of label claim).

Disintegration Test

Disintegration tests carried out on the coated active and coated placebo tablets yielded disintegration times of 2.45 and 2.55 minutes respectively for six tablets.

Dissolution Test

The average results for six coated tablets along with the range of the percentage dissolved is shown in Table 1 and plotted in Figure 1.

Batch Size

The number of 250 mg WR180,409·H_3PO_4 tablets manufactured in Lot WRA-10-02282 was 2102. The number of placebo tablets produced in Lot WRA-11-02283 was 19,694.

Packaging

Twenty-four tablets were placed into 7 dram amber glass vials. The void space was filled with Rayon pharmaceutical coil.

Labels

Labels were prepared as per instructions and are shown in Appendix I, p. I-1 and Appendix II, p. II-1.

Conclusions

The tablet formulations for active WR180,409·H_3PO_4 and matching placebos meet all compendial requirements for tablets.

References

1. The United States Pharmacopeia, XX (1980).

Table 1. Average Percent of WR180,409·H_3PO_4 in solution with time.

Time (Min)	Percent Dissolved ± S.D.
0	0
10	90.6 ± 4.7
20	94.5 ± 3.7
30	96.5 ± 2.6
50	98.1 ± 2.0
70	99.1 ± 1.4
90	99.6 ± 0.8
120	100.0 ± 0

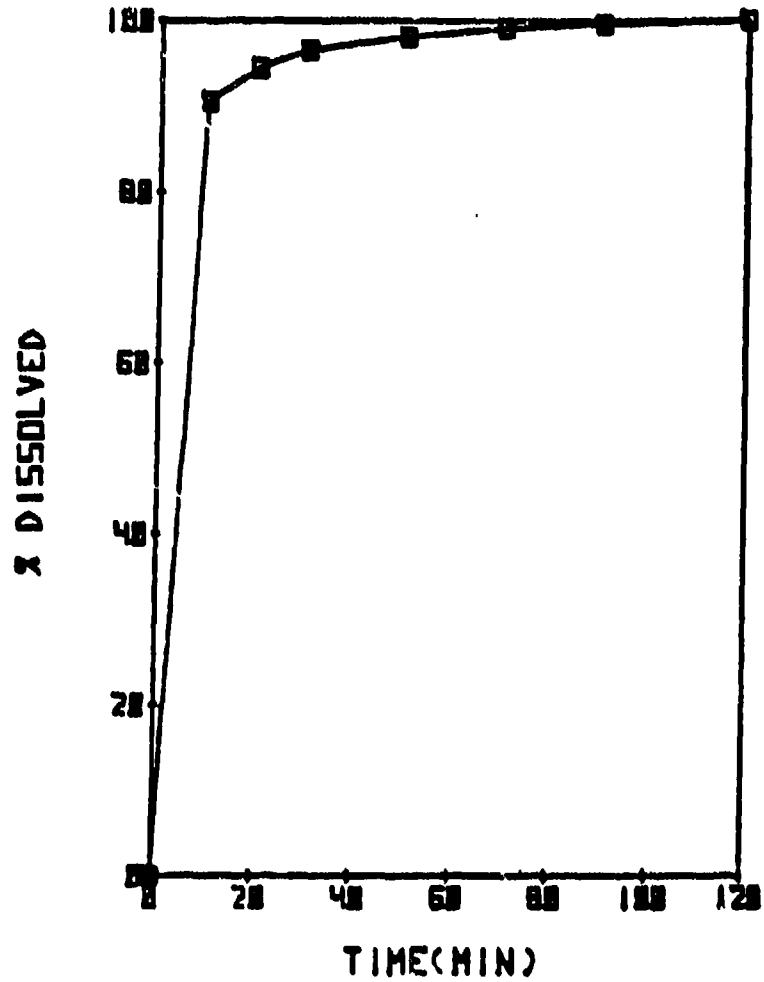

Figure 1. Average dissolution profile of WR180,409·H_3PO_4 coated tablets.

Appendix I

Manufacturing Formula and Quality Control Tests on WR180, 409·H_3PO_4 250 mg Tablets (Lot WRA-10-02283).

Manufacturing Formula

University of Iowa College of Pharmacy — Page 1 of 24 pages

Form CP 1

MANUFACTURING FORMULA

Product WR 180,409.H_3PO_4.AD 250 mg. Tablets	List No. WRA-10
Formula Written by [illegible signature] Date 2/28/83 Formula Checked by [illegible signature] Date [illegible]	Batch Size 2300
Production authorized by [illegible signature]	Control No. WRA-10-02283

Analysis

Assay for	Theoretical	Actual
WR 180,409.H_3PO_4 AD	250 mg.	245.87 mg

Control Assay No. WRA-93-033 Worksheet Checked by [illegible signature] Date 4.8.83

Specifications

	Initial	Theoretical	Actual
Size	[illegible]	7/16 inch deep cup	7/16 inch deep cup
Weight	[illegible]	315 ± 20 mg.	315.6 mg
Color	[illegible]	Green	Green
Disintegration	[illegible]	NMT 15 minutes	2.45 min
Tablet Hardness	[illegible]	> 9 Kp	11.4 Kp
Tablet Thickness			
Clarity			
pH			
Density			
Viscosity			
Sedimentation			
Gross Appearance			
Sterility			
Pyrogens			
Other Weight variation (See attached sheet)	[illegible]	USP	USP

Package and Label

Type of Container Amber glass vials

Size of Container 2 dram

Method of Packaging Tablets were packaged using the Versacount.

Remarks

WALTER REED ARMY INSTITUTE OF RESEARCH

Division of Experimental Therapeutics

Washington D.C. [illegible]

WR 180,409 [illegible] AD [illegible] 250 mg 24 Tablets

[illegible]

Control No. WRA 10-02283

Manufactured [illegible] Bottle № 2-0-0

CAUTION [illegible]

Manufactured by [illegible] College of Pharmacy

The University of Iowa [illegible]

Packaged by [illegible signature]

Date 3/26/83

Page 2 of 24 Pages

Product WR 180,409; H_3PO_4-AD; 250 mg Tablets Batch No. WRA-10

Batch Size 7300 Control No. WRA-10-022(R)

Instruction or Special Instructions

507

EACH CONTAINS	INGREDIENTS AND DIRECTIONS	RAW MAT'L CONTROL NO.	INITIAL		AMOUNT PER BATCH
250 mg	1. Weigh 570 gm of WR 180,409; H_3PO_4-AD and transfer it to the 8 qt. V-blender.	HM-021-096	PL	WRA	380.2 gms
	Add to the same V-blender:				
97.3 mg	2. 201.33 gms of Avicel PH 101.	HM-021-194	PL	WRA	201.33 gms
53 mg	3. 172.5 gms of Lactose.	SA-112-042	PL	WRA	172.5 gms
3.3 mg	4. 5.75 gms of Magnesium Stearate.	DD-042-096	PL	WRA	5.75 gms
	5. Blend the powder for two minutes and slug the powder blend using Colton rotation tablet machine (Hardness 10-12 to 14 kg.)		PL	WRA	
	6. Break up the slugs and pass it through a 20 mesh screen.		PL	WRA	
	7. Weigh the amount of screened powder and transfer it to the 8 qt. V-blender. Weight of the powder blend = 575 gms.		PL	WRA	
	8. Add to the powder blend (7):		PL	WRA	
97.3 mg	9. 201.33 gms of Avicel PH 101.	HM-021-194	PL	WRA	201.33 gms
10 mg	10. 21.0 gms of Amberlite IRP 88.	HM-021-058	PL	WRA	21.0 gms
3.3 mg	11. 5.75 gms of Magnesium Stearate.	DD-042-096	PL	WRA	5.75 gms
	12. Blend the mixed powder for two minutes with half the amount of magnesium stearate and then again for two minutes with rest of the magnesium stearate.		PL	WRA	
	13. Punch the tablets using 7/16 inch deep concave punches on Colton 4-station tablet machine. Tablet weight for ten tablets should be between 6.69 to 7.61 gm.		PL	WRA	
	14. Clean the tablets and prepare for coating.		PL	WRA	
	15. Yield: Total wt. of the finished tablet = 1.08 kg (Av. wt. of the tablet = 511.6 mg) = 2108 tablets				
	# of 7 dram vials filled: 82 e.g. tablet/vial = 24				
	# of tablets packaged = 82 × 24 = 1968				

In-Process Weight Variation

Page 3 of 24 Pages

Product WH 180,409 H_3PO_4 AD, 250 mg. Tablets Lot No. WRA-10

Batch Size 2100 Control No. WRA-10-023(3)

Addition or Special Instructions

OIL CONTAINS	INGREDIENTS AND DIRECTIONS	RAW MAT'L CONTROL NO.	INITIAL	AMOUNT PER BATCH
	IN-PROCESS CONTROL			
	Grams (Range) Hardness (3.9 KP) Thickness (in mm)			
	9.19 - 9.41 gm (10 tablets)			
	9.31 10.4 9.15			
	9.16 10.6 9.17			
	9.31 11.6 9.16			
	9.17 11.6 9.16			
	9.29 11.4 9.31			
	9.16 11.9 9.15			
	9.15 10.6 9.16			
	9.19 11.6 9.17			
	9.21 11.4 9.19			
	9.11 11.1 9.29			
	9.16 11.1 9.16			
	9.14 10.4 9.14			
	9.19 N.D 9.21			
	average 11.4 KP 9.15 mm			

Blend

9 Tablet green ☆ Dr. Chen's 75

one packed bottle 9 11 tablet

Purity

Purity of WR 180,409·H_3PO_4 Lot AD

Taken as 99.1% from SRI Report No. 293

The University of Iowa
Iowa City, Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4520

1847

IN-PROCESS CONTROL
(Analysis of Powder Mix)

Item: WR180,409, H_3PO_4 tablets, 250 mg.

Lot No.: WRA-10-02283

Quantitative UV Analysis: 249.46 mg/515 mg.

Test Result: OK

Amount of Retained Sample: 10.0 gm.

Control No.: WRA-087-033

T. F. Collins

The University of Iowa
Iowa City, Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4520

Weight Variation of Finished Tablets

1847

WEIGHT VARIATION OF FINISHED TABLETS

Item: WR180,409·H_3PO_4, 250 mg tablets

Lot No.: WRA-10-02283 (uncoated)

No.	mg/tablet	No.	mg/tablet
1	504	11	515
2	509	12	513
3	496	13	512
4	512	14	519
5	518	15	509
6	513	16	516
7	515	17	504
8	514	18	515
9	512	19	526
10	523	20	527

Average Weight: 513.6 mg/tablet

Deviation from low (496 mg) = 3.43%

Deviation from high (527 mg) = 2.6%

Control No.: WRA-90-033

T. F. C Lin

The University of Iowa
Iowa City Iowa 52242

Content Uniformity of Finished Product

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4520

1847

CONTENT UNIFORMITY

Item: WR180,409, H_3PO_4, 250 mg. tablets

Lot No.: WRA-10-02283 (uncoated)

No.	mg. labelled amount
1	245.62
2	251.50
3	247.39
4	243.28
5	249.15
6	247.98
7	246.80
8	228.00
9	246.80
10	249.15 mg

Average amount 245.57 mg/tablet

Deviation from low (228.0 mg.): 7.2%

Deviation from high (251.5 mg.): 2.4%

Control No.: WRA-93-033

T. F. Chen

The University of Iowa
Iowa City Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4520

DISINTEGRATION TEST

Item: WR180,409, H_3PO_4, 250 mg. tablets (coated)

Lot No.: WRA-10-02283

Medium: 900 ml distilled water

Temperature: 37°C

Apparatus: USP XX, p. 958

Time: 2.45 minutes

Control No.: WRA-98-033

T.F. Oh

The University of Iowa
Iowa City, Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4920

Dissolution Test Results

DISSOLUTION

Item: WR 180,409.H_3PO_4 AD, 250 mg. tablets (coated)

Lot No.: WRA-10-02283

Apparatus: USP XX, dissolution apparatus 1, p.959

Medium: 1000 ml 0.1N HCl

Temperature: 37°C

Speed: 100 rpm

Time(min)	% dissolved	Time(min)	% dissolved
10	88.45	10	95.15
20	93.00	--	--
30	96.30	30	97.80
50	97.40	50	99.60
70	98.60	70	99.80
90	99.23	90	100.00
120	100.00	120	100.00

T. F Chi

...cont.

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Iowa City, Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4520

....cont.

Time(min)	% dissolved	Time(min)	% dissolved
10	93.50	10	94.40
20	96.70	20	97.50
30	96.30	30	98.70
50	98.80	50	99.80
70	99.40	70	100.70
90	99.70	90	100.50
120	100.00	120	100.00

Time(min)	% dissolved	Time(min)	% dissolved
10	89.43	10	82.90
20	96.50	20	88.70
30	98.20	30	91.50
50	98.70	50	94.50
70	99.40	70	96.60
90	99.80	90	98.30
120	100.00	120	100.00

Control No.: WRA-96-033

T. F. Co

Data Sheets for Specifications of Excipients

WR 180,409·H_3PO_4, Walter Reed Army Institute of Research

Lot AD

PS # M-960-017-960

Identification Test: Passed

Infra red and ultra-violet spectrum

HH-023-096

Lot WRA-10-02283

Avicel PH 101, FMC, Lot 1301

PS # M988-017-988

Identification Test: Passed

HH-023-124

(Certificate of analysis attached)

FMC CORPORATION
Food & Pharmaceutical Products Division
1301 Ogletown Road
Newark, Delaware 19711

PRODUCT QUALITY CONTROL REPORT

PRODUCT: AVICEL PH-101
Microcrystalline Cellulose, N.F.

LOT NO: 1301
DATE : 1/10/83

Identification	Conforms to NF
Loss on Drying, %	3.6 - 4.1
Heavy Metals, ppm	<10
Residue on Ignition, ppm	45
Water Soluble Substances, mg/5g	4.5
Particle Size, WT. % + 60 mesh	<0.1
WT. % + 200 mesh	15 - 23
pH	6.1
Assay, % cellulose	98.8
Starch Test	negative
Retained on a screen having 37 um openings, wt. %	>5
Identification	passes

R. B. Wortz

R. B. Wortz
Quality Control Manager

Lactose, U.S.P., Hydrous, Sheffield, Lot 2NB24

PS # M808-017-808

Identification Test: Passed

GG-112-092

(Certificate of analysis attached)

SHEFFIELD PRODUCTS | PROTOCOL OF ASSAY

CUSTOMER: UNIVERSITY OF IOWA
ADDRESS: COLLEGE OF PHARMACY
IOWA CITY IOWA 52242
ATTN MARY HANSEN

PRODUCT: LACTOSE U.S.P. HYDROUS NOR

LOT NO.: 2N926 | DATE SHIPPED:
CUSTOMER ORDER NO.: | NUMBER OF DRUMS:
| INVOICE NO.:

RESULTS OF ASSAY WHERE APPLICABLE TO PRODUCT SHIPPED:

CHEMICAL/PHYSICAL		MICROBIOLOGICAL	
SOLUBILITY	PASS	STAND. PLATE COUNT	<100/GRAM
MOISTURE %	5.22 * 5.22	THERMOPHILE COUNT	PASS
ASH %	0.05%	E. COLI	NEGATIVE
HEAVY METALS	45 PPM	SALMONELLA	NEGATIVE
SPECIFIC ROTATION	55.39	MOLD	<50/GRAM
ACIDITY	PASS		
PH (10% SOL.)	4.3 * 4.4		
ALCOHOL SOL. RESIDUE	1.2%		
COLOR	PASS		
CLARITY OF SOLUTION	PASS		

DATE: 03/19/82

SHEFFIELD PRODUCTS, BOX 630, NORWICH, NY 13815 KRAFT INC.

Magnesium Stearate, N.F., Mallinckrodt, Lot KMSZ

PS # M364-017-364

Identification Test: Passed

DD-042-096

(Certificate of analysis attached)

Mallinckrodt, Inc.

PARIS, KENTUCKY • P.O. BOX [illegible] • [illegible]

ITEM - MAGNESIUM STEARATE NF

CODE 2256

LOT KMSZ

TESTS	[illegible]
Identification	Passes test.
Loss on drying	4%.
Lead (Pb)	Less than 0.00017
Assay (MgO)	7.7%
Sieve test US Standard #325 Mesh	99.6% thru

It is hereby certified that the [illegible] analysis of the subject item.

Ted Dubowski
Manager Quality Control
Mallinckrodt, Inc.
Paris, Kentucky

js 7-8-82

Amberlite IRP-88, Rohm & Haas, Lot 31040

PS # M949-017-949

Identification Test: Passed for Potassium

HH-023-085

(Certificate of analysis attached)

ROHM AND HAAS COMPANY
INDEPENDENCE MALL WEST
PHILADELPHIA PENNSYLVANIA 19105

University of Iowa
Attn: John Jordan
College of Pharmacy
Iowa City, IA 52242
(319-353-4520)

DATE 1/29/83

REFERENCE

WE ARE SENDING YOU THE ITEMS DESCRIBED BELOW
☐ FOR OUR FILES ☐ FOR YOUR FILES ☐ FOR YOUR APPROVAL
☐ MEMO

Needs Certificate of Analysis on Lot # 31040

REQUIRED SHIP DATE

SALES OFFICE: Home Office
SALESMAN
DELIVERY INSTRUCTIONS

PLANT	PRODUCT CODE	DEPT		QUANTITY	NET WEIGHT	PRODUCT NAME
03	6-9235	16		2	1 lbs.	Amberlite IRP-88
	ANALYTICAL INFORMATION:					
	Lot Number being shipped					3-1040
	~~Moisture~~					~~6.1~~
	Potassium Sulfate					51.5
	Sodium					.07
	~~Heavy Metals:~~					
	Iron					4 ppm
	Lead					3 ppm
	~~Chromium~~					~~less than 1 ppm~~
	Nickel					less than 1 ppm
	Particle Size:					
	~~Retained on 100 mesh~~					0
	Retained on 200 mesh					16.
	Retained on 325 mesh					48.5

YOUR INTEREST IN OUR PRODUCTS IS APPRECIATED. IF YOU HAVE ANY QUESTIONS REGARDING OUR PRODUCTS, PLEASE CONTACT OUR SALES OFFICE NEARLY YOU. WE WILL BE GLAD TO GIVE YOU ADDITIONAL INFORMATION. THE ADDRESSES AND TELEPHONE NUMBERS ARE SHOWN ON THE REVERSE SIDE.

S. Terrell Ext. 244

FORM 20618 (P-1)

CUSTOMER COPY

ROHM AND HAAS DELAWARE VALLEY INC.

June 10, 1982

Amberlite IRP-88

(Polacrilin Potassium NF)

Amberlite IRP-88, a weakly acidic cation exchange resin in the potassium form used as a tablet disintegrant in pharmaceutical preparations, is covered by a Monograph in the National Formulary as Polacrilin Potassium NF. More specifically, the Monograph will be found on page 380 of Supplement 3, USPXX/NF XV.

The attached specification values apply to Amberlite IRP-88 and are in compliance with the compendial specifications in USPXX/NF XV. If you require additional information concerning this material, please contact Gerald D. Button at our corporate address, Independence Mall West, Philadelphia, Pennsylvania 19105. Mr. Button's telephone number is (215) 592-3698.

Yours truly,

Boris Guthezahl

Boris Guthezahl, PhD.
Quality Control Manager

BG:car

ROHM AND HAAS COMPANY

Customer Specifications for Amberlite IRP-88 (Polacrilin Potassium NF)

	Minimum	Maximum
Loss On Drying	—	10%
Particle Size		
Retained on #100 Sieve (U.S. Standard)	—	1%
Retained on #200 Sieve (U.S. Standard)	—	30%
Potassium as Potassium Sulfate	46%	56%
Sodium	—	0.2%
Heavy Metals	—	20 ppm
Iron	—	100 ppm
*Arsenic	—	3 ppm

Note: These specifications are consistent with the compendial specifications as presented in USPXX/NF XV, Supplement 3.

*Rohm and Haas Company does not analyze Amberlite IRP-88 routinely for arsenic. A great deal of historical data shows that there is essentially no arsenic in this product.

Boris Guthezahl

Boris Guthezahl, PhD.
Quality Control Manager

[illegible]ar
June 10, [illegible]

The University of Iowa
Iowa City Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4520

APPROVAL FOR SHIPMENT FORM

Product Name: WR-190,409

Lot Number: WRA-10-02283

Container Size: 7 dram Amber Glass Vials

Dosage Form: Tablets

Acceptable Container: 83

Rejects: 0

Total Units Shipped: 83 x 24

Date Shipped: 29 March 1983

Name and Address of Receiver:

Dr. Larry Fleckenstein

Forest Glen Annex; Bldg. 500; Brookville Rd.

Walter Reed Army Institute of Research

Silver Spring, MD 20910

Approval of Shipment by: [signature]

Pharmaceutical Services
College of Pharmacy

University of Iow
Iowa City, Iowa

PRODUCT RELEASE FORM

Part

Product: WR180,409·H_3PO_4 250 mg tablets

Lot No.: WRA-10-02283

Batch Size: 2300 tablets

Date Received by Warehouse: _____

Quantity	Size

Warehouse: Place this product in quarantine. Please match this form with the release form before placing the product in use.

Part A remains with product until released.

(Detach along dotted line)

PRODUCT RELEASE FORM

Part

Part B remains with Quality Control Department Analysis Sheets

Product: WR180,409·H_3PO_4 250 mg tablets

Lot No.: WRA-10-02283

Batch Size: 2300 tablets

Warehouse: Please (release, ~~destroy, return to mfg.~~) this product and remove from quarantine.

Signature: Ling-Tong Chi

Date Released: 3-28-83

SECTION II

Manufacturing Formula and Quality Control Tests on NP181, 4[illegible]-H-PD, Placebo Tablets (Lot NDA-11-02283).

Manufacturing Formula

University of Iowa College of Pharmacy Page 1 of 11 pages

MANUFACTURING FORMULA

Product Placebo Tablets for WR 180,409 HyPOs AD Lot No. WRA-11

Formula written by [illegible] Date 4/14/83 Formula checked by [illegible] Date 4/14/83 Batch Size 30,000

Production supervised by [illegible] Control No. WRA-11-00283

Analysis

Assay for	Theoretical	Actual
[illegible] HyPOs AD	Absent	[illegible]

Control Lot No. WRA 83-031 Analysis performed by J.E. Collins Date 4.8.83

Specifications

	Initial	Theoretical	Actual
Size		¼ inch deep cup	¼ inch deep cup
Weight		512 ± 26	512.46 mg
Color		Green	Green
Disintegration		NMT 15 minutes	3.55 minutes
Tablet Hardness		7 Kp	10 Kp
Tablet Thickness			
Friability			
Moisture			
Sedimentation			
Gross Appearance			
Sterility			
Pyrogen			
Other weight variation (See attached sheet)		USP	USP

Package and Label

Type of Container Amber glass vials

Size of Container 30 DR

Method of Packaging Tablets were packaged using the Versacount.

Remarks

Packaged by [signature]

Date 5/12/83

WALTER REED ARMY INSTITUTE OF RESEARCH
Division of Experimental Therapeutics
Washington D.C. 20012

WR-180,409 ◎ HyPOs AD 84-00479 Placebo 24 Tablets

Control No. WRA 11 00283 Name No. 200

Manufactured 2-83

CAUTION: New Drug—Limited by Federal Law to Investigational Use Only

Manufactured by Pharmaceutical Services ◎ College of Pharmacy ◎ The University of Iowa ◎ Iowa City Iowa 52242

... Tablets for MK 180,109.0,[illegible] AU ... List No. ... MKA-11

... Size 20,000 ... Control No. MKA-11-022R1

... or Special Instructions

PAINS	INGREDIENTS AND DIRECTIONS	RAW MAT'L CONTROL NO.	INITIAL	AMOUNT PER BATCH
	Weigh			
	[illegible] of Microcrystalline [illegible]	[illegible]		
	[illegible] of Lactose	[illegible]		
	[illegible] of Aperlite IR-88	MM-001-015		
	[illegible] of Magnesium Stearate	DD-001-014		
	and transfer it to the 1 cubic feet stainless steel V-blender.			
	5. Blend the powder for two minutes.			
	6. Weigh [illegible] of Magnesium Stearate and mix it for another two minutes.	DD-001-014		
	7. Punch the tablets using 5/16 inch punches on Colton rotation tablet machine.			
	8. Clean and package the tablets in bulk.			
	9. Yield:			
	# of units packaged: 42			
	84 TABS / unit			
	Total # of tablets packaged: 1000 TABS			
	* Remaining ~19,000 TABS were used for experimental runs and were destroyed			

In-Process Weight Variation

Pg. 1 of 21 Pages

Product Placebo Tablets for MR 180+09.H_3PO_4 AD Lot No. MRA-1[illegible]

Batch Size 20,000 Control No. MRA-11-02283

Direction or Special Instructions

CONTAINS	INGREDIENTS AND DIRECTIONS	RAW MAT'L CONTROL NO.	INITIAL	AMOUNT PER BATCH

IN-PROCESS CONTROL

[illegible]	[illegible]	[illegible]
([illegible])	([illegible])	[illegible]
[illegible]		
9.14	9.7	9.31
9.13	10.2	9.40
9.17	9.4	9.40
9.15	10.2	9.15
9.14	9.4	9.15
9.10	11.4	9.40
9.11	10.4	9.40
9.10	10.4	9.40
9.13	9.4	9.17
9.14	10.4	9.15
9.17	10.4	9.40
9.11	11.1	9.40
9.15	10.4	9.40
9.14	11.4	9.15
9.16	9.8	9.40
9.14	11.4	9.40
9.14	10.4	9.40
9.11	11.0	9.15
9.15	9.8	9.35
9.17	9.4	9.40
9.17	9.4	9.40
9.15	10.2	9.40
9.13	10.4	9.35
9.15	11.4	9.35
9.10	9.8	9.15
9.10	10.4	9.15
9.14	10.8	9.15
9.11	9.3	9.35
9.15	11.0	9.40
9.14	11.0	9.40
	10.24	9.29 mm

1866

The University of Iowa
Iowa City, Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4520

IN-PROCESS CONTROL

Item: Placebo tablets for WR180,409,H_3PO_4

Lot No.: WRA-11-02283

Quantitative Analysis: WR180,409,H_3PO_4 wasn't detected

Control No.: WRA-89-033

T. F. Chiu

The University of Iowa
Iowa City Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4520

Weight Variation of Finished Tablets

WEIGHT VARIATION OF FINISHED TABLETS

Item: Placebo tablets for WR180,409,H_3PO_4

Lot No.: WRA-11-02283

No.	mg/tablet	No.	mg/tablet
1	529	11	521
2	516	12	508
3	522	13	525
4	538	14	549
5	515	15	525
6	524	16	525
7	518	17	513
8	542	18	525
9	506	19	526
10	519	20	513

Average Weight: 522.95 mg/tablet

Deviation from low (506) = 3.25%
Deviation from high (549) = 4.97%

Control No.: WRA-99-033

T. F. Cline

The University of Iowa
Iowa City Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4520

DISINTEGRATION TEST

Item: Placebo tablets for WR180,409,H_3PO_4 (Coated)

Lot No.: WRA-11-02283

Medium: 900 ml distilled water

Temperature: 37°C

Apparatus: USP XX, p. 958

Time: 2.55 minutes

Control No.: WRA-98-033

II-7

Data Sheets for Specifications of Excipients

Avicel PH 101, FMC, Lot 1301

PS # M988-017-988

Identification Test: Passed

HH-023-124

(Certificate of analysis attached)

II-8

FMC CORPORATION

Food & Pharmaceutical Products Division

1301 Ogletown Road

Newark, Delaware 19711

PRODUCT QUALITY CONTROL REPORT

PRODUCT: AVICEL PH-101
Microcrystalline Cellulose, N.F.

LOT NO: 1301
DATE : 1/10/83

Identification	Conforms to NF XV
Loss on Drying, %	3.6 - 4.1
Heavy Metals, ppm	<10
Residue on Ignition, ppm	45
Water Soluble Substances, mg/5g	4.5
Particle Size, WT. % + 60 mesh	<0.1
WT. % + 200 mesh	15 - 23
pH	6.1
Assay, % cellulose	98.8
Starch Test	negative
Retained on a screen having 37 um openings, wt. %	>5
Identification	passes

R. B. Wortz

R. B. Wortz
Quality Control Manager

Avicel PH 101, FMC, Lot 1114

PS # M-684-016-684

Identification Test: Passed

Z-041-018

(Certificate of analysis attached)

FMC CORPORATION
Food & Pharmaceutical Products Division
1301 Ogletown Road
Newark, Delaware 19711

PRODUCT QUALITY CONTROL REPORT

PRODUCT: AVICEL PH-101
Microcrystalline Cellulose, N.F.

LOT NO: 1114
DATE : 4/9/81

Identification	Conforms to NF XV
Loss on Drying, %	3.3-4.4
Heavy Metals, ppm	<10
Residue on Ignition, ppm	41
Water Soluble Substances, mg/5g	5.2
Particle Size, WT. % + 60 mesh	<0.1
WT. % + 200 mesh	11-29
pH	6.4
Assay, % cellulose	98.6
Starch Test	negative
Retained on a screen having 37 um openings, wt. %	>5
Identification	passes

RB Wortz

R. B. Wortz
Quality Control Manager

PURCHASING DEPT.

Lot WRA-11-02283

Lactose, U.S.P., Hydrous, Sheffield, Lot 2NB24

PS # M-808-017-808

Identification Test: Passed

GG-112-092

(Certificate of analysis attached)

SHEFFIELD PRODUCTS — PROTOCOL OF ASSAY

CUSTOMER: UNIVERSITY OF IOWA
ADDRESS: COLLEGE OF PHARMACY
IOWA CITY IOWA 52242
ATTN MARY HANSEN

PRODUCT: LACTOSE U.S.P. HYDROUS 40S

LOT NO.: 2N424
CUSTOMER ORDER NO.:

DATE SHIPPED:
NUMBER OF DRUMS:
INVOICE NO.:

RESULTS OF ASSAY WHERE APPLICABLE TO PRODUCT SHIPPED:

CHEMICAL/PHYSICAL		MICROBIOLOGICAL	
SOLUBILITY	PASS	STAND. PLATE COUNT	<100/GRAM
MOISTURE %	5.22 - 5.22	THERMOPHILE COUNT	PASS
ASH %	0.056	E. COLI	NEGATIVE
HEAVY METALS	<5 PPM	SALMONELLA	NEGATIVE
SPECIFIC ROTATION	55.59	MOLD	<50/GRAM
ACIDITY	PASS		
PH (10% SOL.)	4.5 - 4.9		
ALCOHOL SOL. RESIDUE	1.27		
COLOR	PASS		
CLARITY OF SOLUTION	PASS		

DATE: 03/15/82

SHEFFIELD PRODUCTS, BOX 630, NORWICH, NY 13815 — KRAFT INC.

Lot WRA-11-02283

Magnesium Stearate, N.F., Mallinckrodt, Lot KMSZ

PS # M-364-017-364

Identification Test: Passed

DD-042-096

(Certificate of analysis attached)

Mallinckrodt, Inc.

PARIS, KENTUCKY • P.O. BOX [illegible] • [illegible] • [illegible]

ITLM - MAGNESIUM STEARATE NF — CODE 2256

LOT [illegible]

TESTS	RESULTS
Identification	Passes test.
Loss on drying	3.64.
Lead (Pb)	Less than 0.0001%
Assay (MgO)	7.71
Sieve test US Standard #325 Mesh	99.6% thru

It is hereby certified that the [illegible] analysis of the subject item.

Ted Dunowski
Manager Quality Control
Mallinckrodt, Inc.
Paris, Kentucky

[illegible]

Amberlite IRP-88, Rohm & Haas, Lot 31040

PS # M-949-017-949

Identification Test: Passed for Potassium

HH-023-085

(Certificate of analysis attached)

ROHM AND HAAS COMPANY
INDEPENDENCE MALL WEST
PHILADELPHIA, PENNSYLVANIA 19105

DATE 1/25/93

REFERENCE

WE ARE SENDING YOU [X] THE ITEM(S) CHECKED BELOW
[X] FOR USE IN CHEMICAL ANALYSIS (LABORATORY) [ ] FOR USE IN PRODUCTION [ ] FOR SALE (RESALE)
[ ] OTHER

University of Iowa
Attn: John Jordan
College of Pharmacy
Iowa City, IA 52242
(319-353-4520)

Needs Certificate of Analysis on Lot # 31040

SCHEDULED SHIP DATE

SALES OFFICE: Home Office | SALESMAN | DISTRICT MANAGER

PLANT	PRODUCT CODE	DEPT.		QUANTITY	NET WEIGHT	PRODUCT NAME
03	6-9255	16		2	1 lbs.	Amberlite IRP-88
	ANALYTICAL INFORMATION: Lot Number being shipped					3-1040
	Moisture					6.1
	Potassium Sulfate					51.3
	Sodium					.07
	Heavy Metals:					
	Iron					4 ppm
	Lead					3 ppm
	Chromium					less than 1 ppm
	Nickel					less than 1 ppm
	Particle Size:					
	Retained on 100 mesh					0
	Retained on 200 mesh					16.6
	Retained on 325 mesh					48.6

YOUR INTEREST IN OUR PRODUCTS IS APPRECIATED. IF YOU HAVE ANY QUESTIONS REGARDING OUR PRODUCTS, PLEASE CONTACT OUR SALES OFFICE NEAREST YOU. WE WILL BE GLAD TO GIVE YOU ANY ADDITIONAL INFORMATION. THE ADDRESSES AND TELEPHONE NUMBERS ARE SHOWN ON THE REVERSE SIDE.

S. Tarselli Sa264

FORM 30015 (P. 1)

CUSTOMER COPY

ROHM AND HAAS DELAWARE VALLEY INC.

June 10, 1982

Amberlite IRP-88

(Polacrilin Potassium NF)

Amberlite IRP-88, a weakly acidic cation exchange resin in the potassium form used as a tablet disintegrant in pharmaceutical preparations, is covered by a Monograph in the National Formulary as Polacrilin Potassium NF. More specifically, the Monograph will be found on page 380 of Supplement 3, USPXX/NF XV.

The attached specification values apply to Amberlite IRP-88 and are in compliance with the compendial specifications in USPXX/NF XV. If you require additional information concerning this material, please contact Gerald D. Button at our corporate address, Independence Mall West, Philadelphia, Pennsylvania 19105. Mr. Button's telephone number is (215) 592-3698.

Yours truly,

Boris Guthezahl

Boris Guthezahl, PhD.
Quality Control Manager

BG:car

ROHM AND HAAS COMPANY

Customer Specifications for Amberlite IRP-88 (Polacrilin Potassium NF)

	Minimum	Maximum
Loss On Drying	--	10%
Particle Size		
Retained on #100 Sieve (U.S. Standard)	--	1%
Retained on #200 Sieve (U.S. Standard)	--	30%
Potassium as Potassium Sulfate	46%	56%
Sodium	--	0.2%
Heavy Metals	--	20 ppm
Iron	--	100 ppm
*Arsenic	--	3 ppm

Note: These specifications are consistent with the compendial specifications as presented in USPXX/NF XV, Supplement 3.

*Rohm and Haas Company does not analyze Amberlite IRP-88 routinely for arsenic. A great deal of historical data shows that there is essentially no arsenic in this product.

Boris Guthezahl

Boris Guthezahl, PhD.
Quality Control Manager

RG:car
June 10, 1982

The University of Iowa
Iowa City, Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4520

Approval for Shipment Form

1847

APPROVAL FOR SHIPMENT FORM

Product Name: PLACEBO FOR WR-180,409

Lot Number: WRA-11-02283

Container Size: 7 dram Amber Glass Vials

Dosage Form: Tablets

Acceptable Containers: 42

Rejects: 0

Total Units Shipped: 42 x 24

Date Shipped: 29 March 1983

Name and Address of Receiver:

Dr. Larry Flackenstein
Forest Glen Annex: Bldg. 500: Brookville Rd.
Walter Reed Army Institute of Research
Silver Spring, MD 20910

Approval of Shipment by: [signature]

Product Release Form

Pharmaceutical Services
College of Pharmacy

University of Iowa
Iowa City, Iowa

PRODUCT RELEASE FORM **Part A**

Product: WR180,409·H_3PO_4 Placebo tablets

Lot No.: WRA-11-02283

Batch Size: 20,000 tablets

Date Received by Warehouse: _____

Quantity	Size

Warehouse: Place this product in quarantine. Please match this form with the release form before placing the product in use.

Part A remains with product until released.

(Detach along dotted line)

PRODUCT RELEASE FORM **Part B**

Part B remains with Quality Control Department Analysis Sheets

Product: WR180,409·H_3PO_4 Placebo tablets

Lot No.: WRA-11-02283

Batch Size: 20,000 tablets

Warehouse: Please (release, ~~destroy, return to mfg.~~) this product and remove from quarantine.

Signature: Ing-Tong Chi

Date Released: 3-28-83

Appendix III

Manufacturing Formula for Tablet Coating Solution for WR180,409·H_3PO_4 250 mg Tablets (Lot WRA-10-02283) and Matching Placebos (Lot WRA-11-02283).

III-1
Coating Formula

Page ___ of ___ Pages

COATING PARAMETER BATCH RECORD

Product WR-180-409-HPMC Active + Placebo Tablets Batch Size 13.00 kg

Contractor US Army Walter Reed Army Research Inst. Control Number WRAIR-10-22762

Coating Type Solvent HPMC Color Green

Solids (w/w) ≈4.8 Operator [signature]

Solution Heater ✓ off ____ on ____ temp. setting ____

Pause Controls ✓ off ____ on Settings: Pause 1 ____ Pause 2 ____

Amount of coating solution used (kg) 3.1 kg for seal. Date Coated 3/15/85
of 2 batches

Cautions or Special Instructions:

Coating Formula:

MATERIAL	% w/w	GRAMS	LOT #	CONTROL #	EXP. DATE
HPMC 15 cps	2.6	338	51-P16	BB-101-052	10-21-85
Polyethylene NF 10 cps	0.6	78	63900	II-033-006	3-9-85
Denatured Alcohol USP	32.0	4160	M57458	II-033-017	2-26-85
Methylene chloride	61.5	8000	209614	II-033-016	3-11-85
Opaspray K-1-3135-A	2.9	377	40630	HH-023-100	2-14-85
Triacetin	0.4	52	81-2-10-21-87	BB-101-106	10-30-85

III-2

Polymer Solution for Solvent Film Coating

Form: CR 011581-1 Page One

CAUTION: Prepare film coating Polymer solution/suspension in a well ventilated area, away from flames or sparks.

University of Iowa College of Pharmacy

Polymer Solution for Solvent Film Coating

Contractor Army Product WE-152-409 H3PO4 Aqueous Tablet % Solids

Control # WEA-10-02193 Batch Size 13.02 kg Date Prepared 3/15/93

Add to a clean stainless steel container

Solvent I 8.000 kg.

Solvent: Methylene Chloride, AR Grade

Mfr: J.T Baker Lot #: 209624

Raw Mat'l Lot #: M-030-018-030

Control #: II-033-016 Exp. Date: 3-11-95

EDP #: 5715

Added by: JJ Checked by: _____

Solvent II 4.160 kg.

Solvent: Alcohol USP, Absolute

Mfr: Aaper Lot #: 57459

Raw Mat'l Lot #: M-031-018-031

Control #: II-033-017 Exp. Date: 2-26-95

EDP #: 0225

Added by: JJ Checked by: _____

Solvent III 0 kg.

Solvent: Not Used JJ 3/15/93

Mfr: _____ Lot #: _____

Raw Mat'l Lot #: _____

Control #: _____ Exp. Date: _____

EDP #: _____

Added by: _____ Checked by: _____

Add to the cure container, with mixing

Mixing Started: 11:10 AM Timed by: JWJ

Polymer I 0.339 kg.

Polymer: Hydroxy propyl Methylcellulose 15 cps, N.F.

Mfr: Shinetsu Lot #: 51-P15

Raw Mat'l Lot #: 052-17-052

Control #: GB-101-084 Exp. Date: 12-21-83

EDP #: 9996

Added by: JWJ Checked by:

Polymer II 0.078 kg.

Polymer Ethylcellulose 10 cps N.F.

Mfr: Hercules Lot #: 65900

Raw Mat'l Lot #: M-010-011-020

Control #: II-033-006 Exp. Date: 3-9-85

EDP #: 9996

Added by: JWJ Checked by:

Plasticiser 0.052 kg.

Plasticiser: Tuscetin, Food Grade

Mfr: Eastman Chemical Lot #: P1-2-10-21-81

Raw Mat'l Lot #: M-074-017-074

Control #: GB-101-106 Exp. Date: 10-30-83

EDP #: 9996

Added by: JWJ Checked by:

Additional Non-Coloring Material 0 kg.

Material: Not Used 8/15/83 JWJ

Mfr: Lot #:

Raw Mat'l Lot #:

Control #: Exp. Date:

EDP #:

Added by: Checked by:

[illegible] Control #: [illegible] [illegible]

Additional Non-Coloring Material ___0.___ hr.

Material: Not Used 3/15/83 JW

Mfr: _____ Lot #: _____

Raw Mat'l Lot #: _____

Control #: _____ Exp. Date: _____

EDP #: _____

Added by: _____ Checked by: _____

Mix until a clear solution/unifora suspension is formed.

Mixing stopped: 11.20

Tightly close the container and allow the solution/suspension to set for at lease 2 hours before use.

Rest Time Started: 11.30 AM Stopped: 1.30 PM

Timed by: JW

CAUTION: Prepare solvent film coating solution/suspension in a well ventilated area, away from flames and sparks.

University of Iowa College of Pharmacy

Coating Suspension for Solvent Film Coating

Mix the Color Concentrate Suspension with a high shear mixer for 15 minutes

Mixing Started: 1:15 PM Stopped: 1:30 PM

Timed by: [signature]

Add to a clean, stainless steel container, with mixing

Mixing Started: 1:30 pm

Polymer Solution for Solvent Film Coating 12.623 ~~9.377~~ kg.

Added by: [signature] Checked by: [signature]

Color Concentrate Suspension 0.377 kg.

Mfr: Colorcon Formula # K-1-3335-A

Batch of Lot #: 45630

Raw Material Lot #: M-964-017-964

Control #: HH-283-125 Exp. Date: 2-14-95

EDP #: 9996

Added by: [signature] Checked by: [signature]

Additional Materials 0 kg.

Material NOT Used 3/15/93 [signature]

Mfr: Lot #:

Raw Mat'l Lot #:

Control #: Exp. Date:

EDP #:

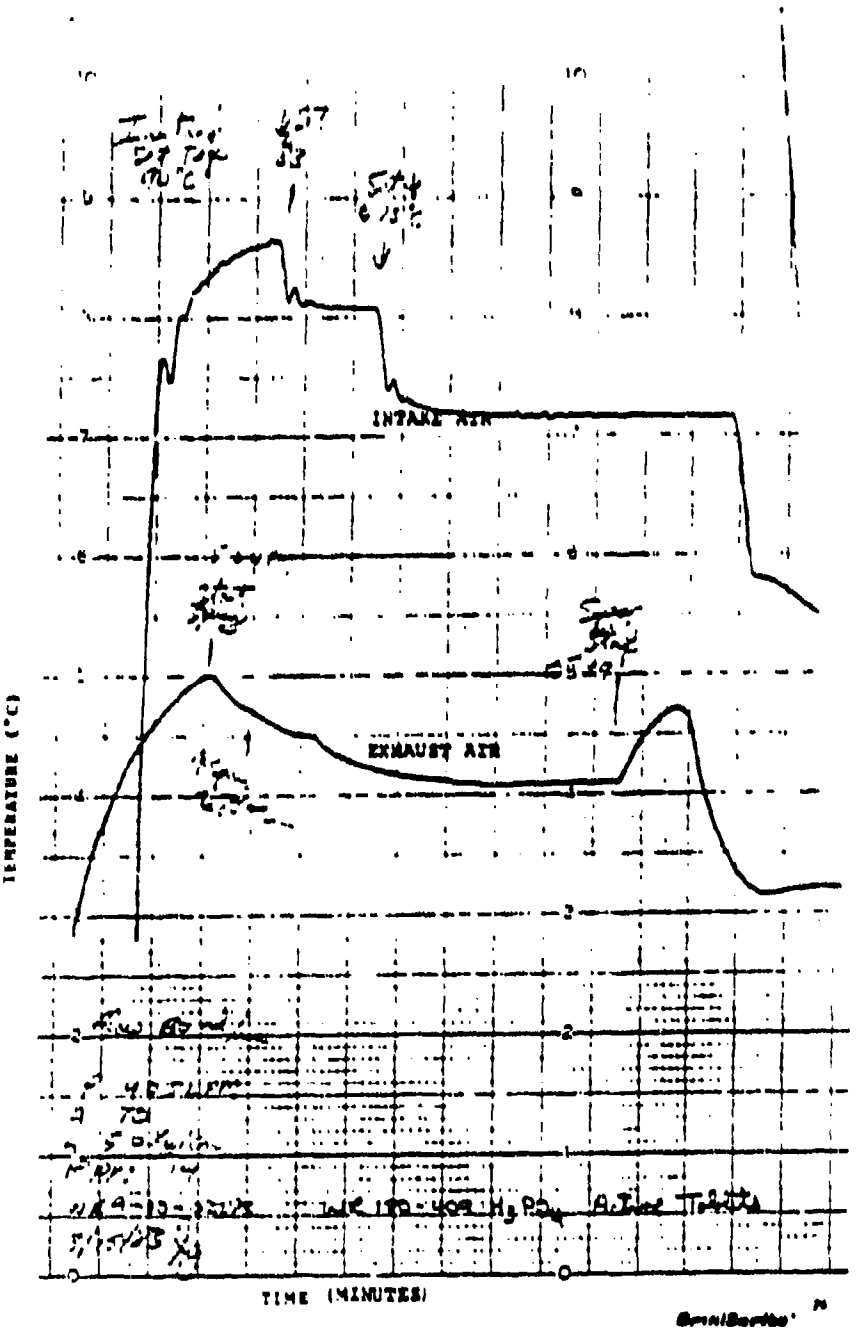
Added by: Checked by:

Mix for 15 minutes.

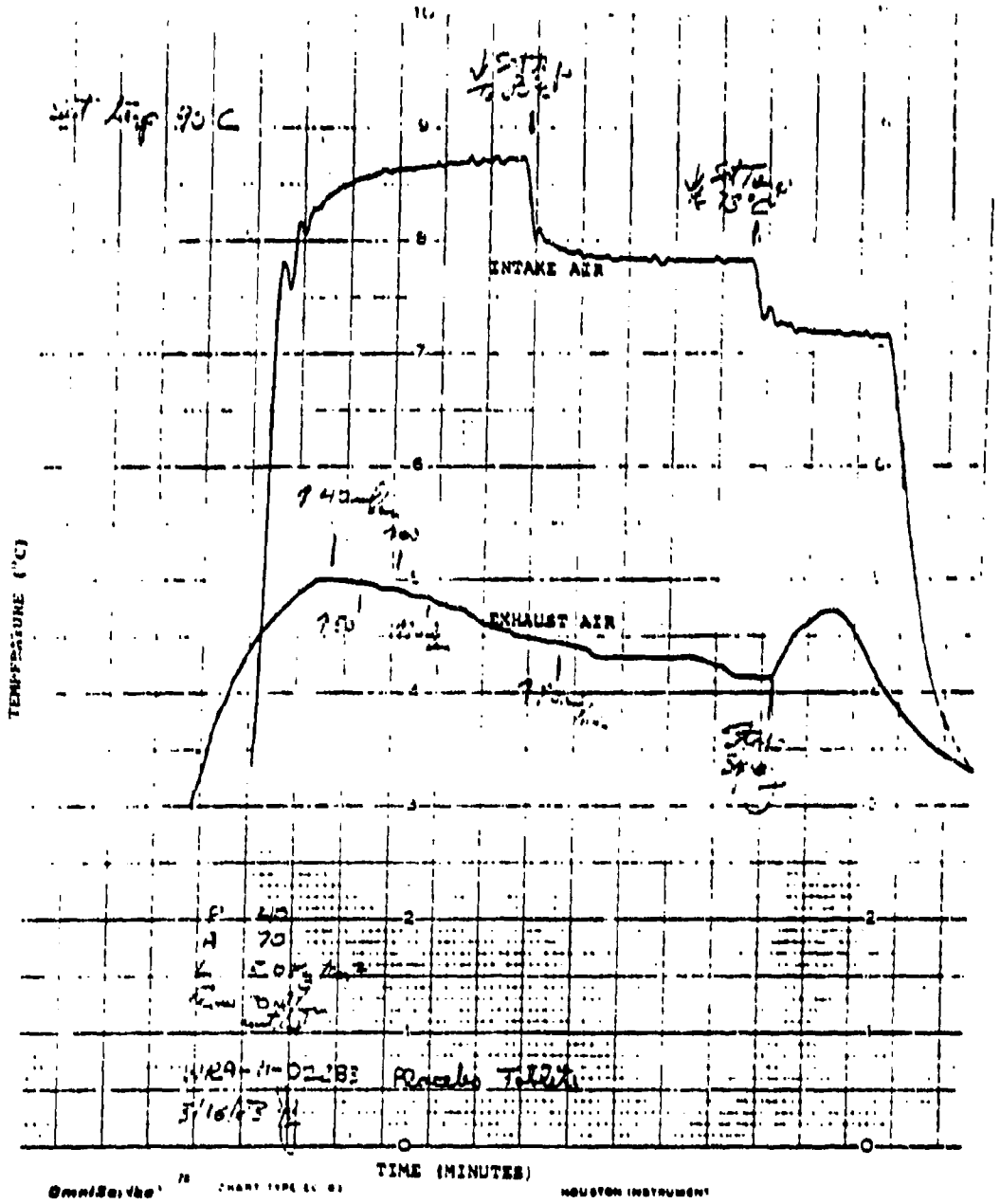
Mixing Stopped: 1:45 PM

Timed by: [signature]

Temperature-Time Spraying Curves



Data Sheets for Specifications of Ingredients



Methylene Chloride, AR Grade, Baker, Lot 209624

PS # M-030-018-030

Identification Test: Passed

II-033-016

Absolute Alcohol, USP, AAPER, Lot #81H28

PS # M-031-018-031

Identification Test: Passed

II-033-017

(Certificate of analysis attached)

AAPER ALCOHOL AND CHEMICAL COMPANY

CERTIFICATE OF ANALYSIS

ATTN: University of Iowa
Purchasing Department
Iowa City, Iowa 52242

ETHANOL PURE 200 PROOF

USP GR.

Lot #81H28
Customer's Order No. Y07991
Date Shipped: 2-24-82

Ethyl Alcohol, Strength	200°
Acidity, %	0.0022
Permanganate Time (min.)	15+
Non-Volatile, %	Passed
Water solubility	Passed
Water insolubles	Passed
Amyl Alcohol & Carbonizables	Passed
Fusel Oil Constituents	Passed
Ketones, Isopropyl Alcohol and Tertiary Butyl Alcohol	Passed
Aldehydes & other foreign organic subs.	Passed
Color, Pt-Co	Passed
Methanol	Passed
Odor	Passed
Suspended matter	Passed

Date: 2-25-82
Analysis No. 1040

T. C. Mathew

T. C. Mathew, Manager, Product Services

This is to certify that the 120, 5 gallon drums (serial numbers 41554-41589, 44660-44695, 44732-44779), Lot #81H28, and 30 Cases of gallons (serial numbers 57453-57482) of 200 proof Pure Ethanol, tax-free meet USP Specifications.

sj

P.O. Box 43049 • Louisville, Ky. 40243 • Telephone 502/423-0655

Hydroxypropyl methylcellulose, USP, Shin-Etsu, Lot 51-816

PS # 052-17-052

Identification Test: Passed

sB-101-084

(Certificate of analysis attached)

[illegible] Plaza, New York, N.Y. 10001

UNIVERSITY OF IOWA
P.O. NO. V05569

CERTIFICATE OF ANALYSIS AND PACKING LIST

1 CARTON GROSS 27 LBS. - NET 10 KILOS

Shin-Etsu Chemical Industry Co., Ltd.

TELEX NO. J24190
ANSWER BACK CODE:
SHINCHEM

6-1, 2-CHOME, OHTEMACHI, CHIYODA-KU,
TOKYO, JAPAN.

TEL. NO. 240-1911
CABLE ADDRESS
"SHINETSUKAGAKU"
TOKYO

January 20, 1977

Analytical Certificate of Pharmacoat 615
(Hydroxypropyl methylcellulose)

Lot No.		51-016
Quantity		10 kilos
Appearance		white powder
Color		white
Oder		practically none
Solution (2% in water)		practically clear
Solution (2% in 55 : 45 CH_2Cl_2-Alcohol)		practically clear
Identification test		pass
Viscosity (2% at 20°C)	(cps)	15.1
Loss on drying	(%)	2.4
Residue on ignition	(%)	0.57
Iron	(ppm)	18.4
Methoxyl content	(%)	28.7
Hydroxy propoxyl content	(%)	8.4

III-13

Ethyl Cellulose, N.F., Hercules, Lot 63900

PS # M-020-018-020

Identification Test: Passed

II-033-006

(Certificate of analysis attached)

HERCULES INCORPORATED

IIb
3/2/83

ANALYSIS REPORT

ETHYL CELLULOSE N.F.

University of Iowa
College of Pharmacy
Iowa City, IA 52242

II 053-006

REPLACEMENT	25145	3/1/83

Type	Lot	Number Containers	Net Each	Net Weight	cps. Viscosity (5% Solids)	% Moisture
N10	63900	1	50	50	8.9	.77

THE ABOVE ANALYSIS WAS DETERMINED ON A REPRESENTATIVE SAMPLE OF THE PRODUCTION LOTS SHIPPED AGAINST YOUR ORDER. THIS ANALYSIS DOES NOT ALTER YOUR OBLIGATION TO EXAMINE AND TEST ALL MATERIAL PRIOR TO USE. FOR DETAILS, PLEASE REFER TO HERCULES TERMS AND CONDITIONS OF SALE (PARAGRAPH 8 FOUND ON THE BACK OF THE ORDER ACKNOWLEDGMENT FORM YOU RECEIVED COVERING THIS SHIPMENT.

NOTE: The above lots comply also with current National Formulary specifications on the basis of manufacturing process validation studies and in-process controls with respect to the following:
(1) Substituent Assay - minimum 44.0% - maximum 51.0% of ethoxyl groups after drying.
(2) Identification tests A and B of current monograph.
(3) Residue on ignition not more than 0.4% (as Na_2SO_4).

3-2-83

HER. 20435 (6-77) 5-00 2M

Triacetin Food Grade, Tennessee Eastman, Lot 81-2-10-21-81

PS # M-074-017-074

Identification Test: Passed

BB-101-106

(Certificate of analysis attached)

October 29, 1981

University of Iowa
College of Pharmacy
Pharmaceutical Service Division
Iowa City, Iowa 52242

Product	Triacetin Food Grade
ECPI Order No.	11167600
Cust Order No.	V87068
Shipping Date	10-21-81
Shipping Cont	1 Drum

Attention: Mr. John Jordan

Gentlemen:

The analysis of the Triacetin Food Grade that we shipped to you is as follows:

Property	TEC Sales Spec. Limits	Analysis
Assay as Triacetin	Min. 98.5%	99.43
Refractive Index 25° C	1.429-1.431	1.4300
Specific Gravity, 25/25° C	1.154-1.158	1.155
Acidity	To Pass Test	Passes
Arsenic (as As)	Max. 3 ppm	<3
Heavy Metals (as Pb)	Max. 10 ppm	<10
Unsaturated Compounds	To Pass Test	Passes
Water	Max. 0.2%	.11

Yours very truly,

D. W. Lane

Quality Assurance
Acid Division

mrd

Opaspray, Formulation # K-1-3335-A, Lot 40630, Coloicon

PS # M-964-017-964

Identification Test: Physical Inspection

Passed
HH-023-100
(Certificate of analysis attached)

QUALITY CONTROL REPORT

PRODUCT NAME: CRASTRA-1

FORMULATION: K-1-3335. A

BATCH NO.: 4063

COLOR: green

TRISTIMULUS DATA:

X	Y	Z
23.9	25.3	6.7

COLOR DIFFERENCE: 2.62

SPECIFIC GRAVITY: 1.08

OTHER

Approved by: L. Cole

Date: 2/11/83

ORIGINAL

QUARTERLY REPORT NUMBER 15

Coating of 250 Mg WR142,490·HCl (Lot AS) Tablets and Formulation and Production of Matching Placebos

Submitted by:

John L. Lach
Douglas R. Flanagan
Lloyd E. Matheson, Jr.

July, 1983

Supported by:

U.S. Army Medical Research and Development Command
Fort Detrick
Frederick, Maryland 21701-5012

Contract DAMD17-79-C-9136

College of Pharmacy
University of Iowa
Iowa City, Iowa 52242

TABLE OF CONTENTS

RESUME' OF PROGRESS

Capsules have been prepared which contain ^{14}C-labelled WR171,669·HCl in combination with polyvinylpyrrolidone (PVP) in either a physical mixture or coprecipitate in a 1:3 ratio. These capsules were produced individually by hand for use in an *in vivo* dog study conducted by WRAIR.

Work has begun on the development of liposomes containing formycin B, 5'-monophosphate. Since this agent is expensive, initial development has been carried out on the structurally similar, but less expensive, inosine monophosphate. Percent entrapment and leakage from the liposome have been studied.

In addition, work is proceeding on the development of a stability-indicating high pressure liquid chromatographic assay for WR249,943 (MMB-4), an oxime with potential use as a nerve gas antidote. In the near future stability studies will be started on this compound.

Objective

The objectives of this work were: 1) to coat existing 250 mg tablets of WR142,490·HCl (Lot AS) supplied by WRAIR and manufactured earlier by Lafayette Pharmacal, Inc. (Lot E-598) and 2) to formulate and produce matching placebo tablets.

Summary

The active 250 mg WR142,490·HCl tablets were coated and matching placebos were formulated and manufactured as described in the batch records.

The weight variation test for the 20 coated active tablets (Lot WRA-12-04013) showed an average weight of 567 mg per tablet with a range from 533 to 580 mg per tablet. The weight variation test for 20 uncoated placebo tablets showed an average weight of 563 mg per tablet with a range from 553 to 573 mg. Weight variation of the coated placebo tablets (Lot WRA-13-04013) showed an average weight of 585 mg per tablet with a range of 575 to 595 mg. USP requirements were met.

Content uniformity was not carried out on the active WR142, 490·HCl tablets since these had been previously tested by Lafayette Pharmacal, Inc. (1). No drug was detected by UV spectrophotometry in the placebo tablets (Lot WRA-13-04013). USP requirements were met.

Disintegration tests carried out on the record active WR142, 490·HCl tablets yielded a time of 4 minutes and 55 seconds for six tablets. This compares to 6.8 minutes for the uncoated tablets as determined by Lafayette Pharmacal, Inc. when these tablets were originally manufactured. Disintegration testing of six placebo tablets yielded a time of 13 minutes.

Dissolution testing carried out on six coated active tablets produced an average percentage of drug dissolved in 60 minutes of 26.8 ± 2.9 (range 22.1 - 29.8%). This compares favorably with a value of 22.4% dissolved in 60 minutes determined previously by Lafayette Pharmacal on the uncoated tablets (1).

Methodology

Formulation Ingredients

Identification tests were carried out on formulation ingredients according to compendial requirements and are reported in Appendices I and III. Certificates of analysis are included. All materials were correct.

Manufacturing Procedure

The coating solution was prepared by placing 5.4 Kg of Water for Injection, USP, into a stainless steel container. To this 0.546 Kg of hydroxypropyl methylcellulose, USP and .054 Kg of polyethylene glycol 400, N.F. were added with mixing. Mixing continued for two hours until a clear, uniform solution was obtained. The container was closed and allowed to stand for one hour before use. The active and placebo tablets were film coated using a Freund Model HCT-48 Hi-Coater. The temperature-time curves for the coating process are included in Appendix I.

The matching placebo tablets (WRA-13-04013) were produced by mixing 4.21 Kg of anhydrous lactose, USP; 0.60 Kg of Avicel PH 101; and 0.55 Kg of Sta-Rx 1500 in a V-Blender for 10 minutes 0.055 Kg of magnesium stearate was added and blending continued for 5 minutes. Subsequently, 0.110 Kg of talc was added and mixing continued for 5 minutes. The tablets were punched on a Manisty single punch tablet machine using a 7/16 inch standard concave punch and die set. Procedures are described in detail in Appendix III.

The active 250 mg WR142,490·HCl tablets (Lot AS) supplied by WRAIR and manufactured by Lafayette Pharmacal (Lot E-598) were coated using the same batch of colorless coating solution used to coat the placebo tablets.

USP Methods and Requirements

The weight variation test for uncoated tablets is described in USP XX (1). Twenty tablets must be individually weighed and the individual weights of not more than two tablets can differ from the average weight by not more than 5% for tablets weighing more than 324 mg. No single tablet can differ by more than 10%. This test was conducted on coated active and coated and uncoated placebo tablets using a Mettler H51AR semimicro balance according to the USP XX requirements. Coated tablets are exempt from USP weight variation specifications.

The disintegration test for tablets is described in USP XX (1). Six coated tablets from both the active and placebo lots were tested using 900 cc of distilled water for the placebo tablets and 900 cc of simulated gastric fluid for the active tablets as the medium at a temperature of 37°C.

The dissolution test for tablets is described in USP XX (1). Six coated tablets (WRA-12-04013) were tested using dissolution apparatus number one, 900 ml of 0.1 N HCl, a temperature of 37°C and a rotational speed of 50 rpm.

Results

Weight Variation Test

The weight variation test for the 20 coated active tablets (Lot WRA-12-04013) showed an average weight of 567 mg per tablet with a range from 533 to 580 mg per tablet. The data are shown in Appendix II, p. II-2. The weight variation test for 20 uncoated placebo tablets showed an average weight of 563 mg per tablet with a range from 553 to 573 mg. The data are shown in Appendix III, p. III-5. Weight variation of the coated placebo tablets (Lot WRA-13-04013) showed an average weight of 585 mg per tablet with a range of 575 to 596 mg. The data are shown in Appendix III, p. III-6.

Content Uniformity

Content uniformity was not carried out on the active WR142, 490·HCl tablets since these had been previously tested by Lafayette Pharmacal, Inc. (1). No drug was detected by UV spectrophotometry in the placebo tablets (Lot WRA-13-04013).

Disintegration Test

Disintegration tests carried out on the coated active WR142, 490·HCl tablets yielded 4 minutes and 55 seconds for six tablets. This compares to 6.8 minutes for the uncoated tablets as determined by Lafayette Pharmacal, Inc. when these tablets were originally manufactured (1). Disintegration testing of six placebo tablets yielded a time of 13 minutes.

Dissolution Test

Dissolution testing carried out on six coated active tablets produced an average percentage of drug dissolved in 60 minutes of 26.8 ± 2.9 (range 22.1 - 29.8%). Data are shown in Appendix II, p. II-4. This compares favorably with a value of 22.4% in 60 minutes determined previously by Lafayette Pharmacal on the uncoated tablets (1).

Batch Size

The number of active tablets coated was 5775 (Lot WRA-12-04013). The number of placebo tablets produced in Lot WRA-13-04013 was 10,000 with a yield of 9325.

Packaging

A PEI Versacount Tablet Counter was used to place 25 tablets into each 7 dram amber glass vial. The void space was filled with Rayon pharmaceutical coil.

Labels

Labels were prepared as per instructions and are shown in Appendix II, p. II-1 and Appendix III, p. III-1.

Conclusions

The active and placebo tablets meet all compendial requirements for tablets.

References

1. The United States Pharmacopeia, XX (1980).

Apperdix I

Manufacturing Formula for Tablet Coating Solution for WR142,490·HCl 250 Mg Tablets (Lot WRA-12-04013) and Matching Placebos (Lot WRA-13-04013).

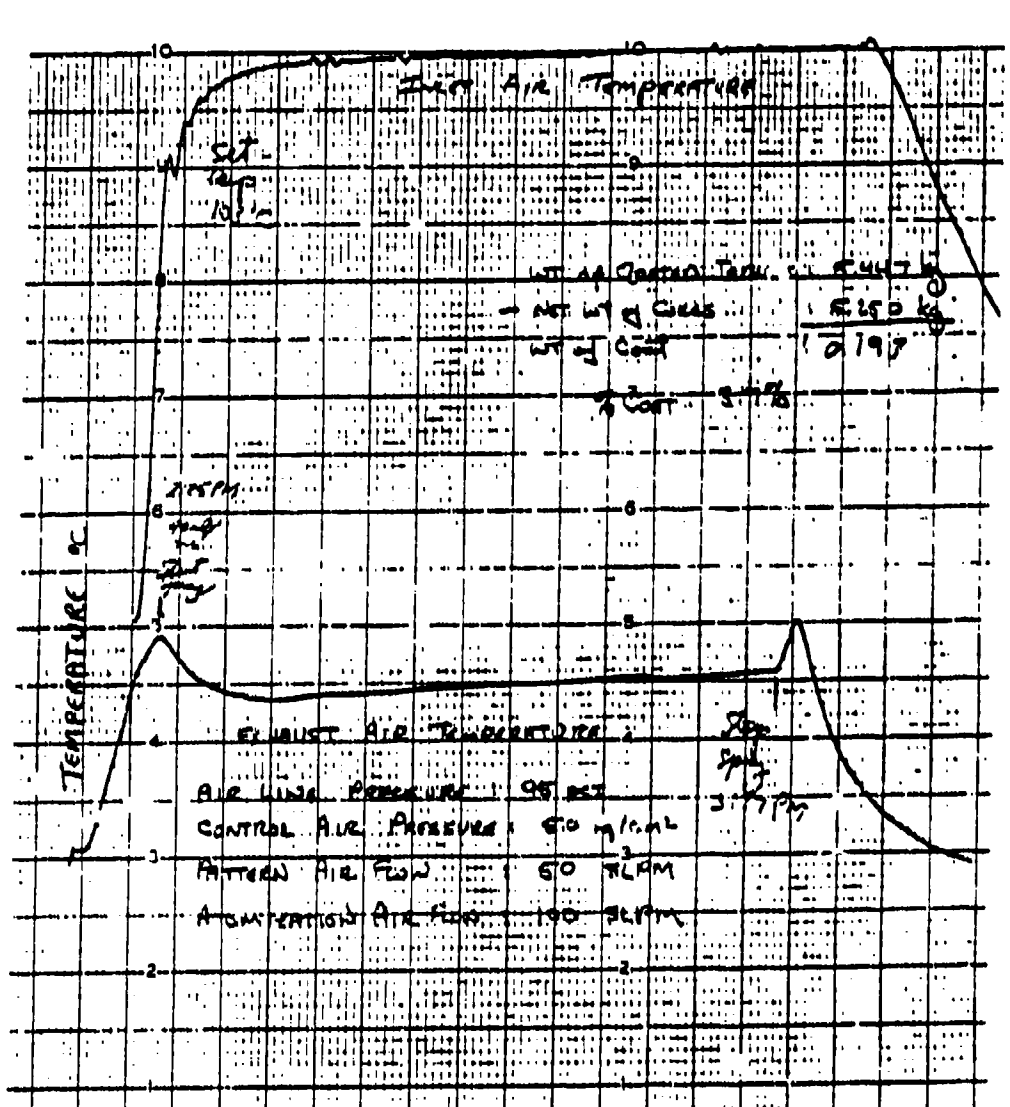
Coating solution for Sertraline Slowly

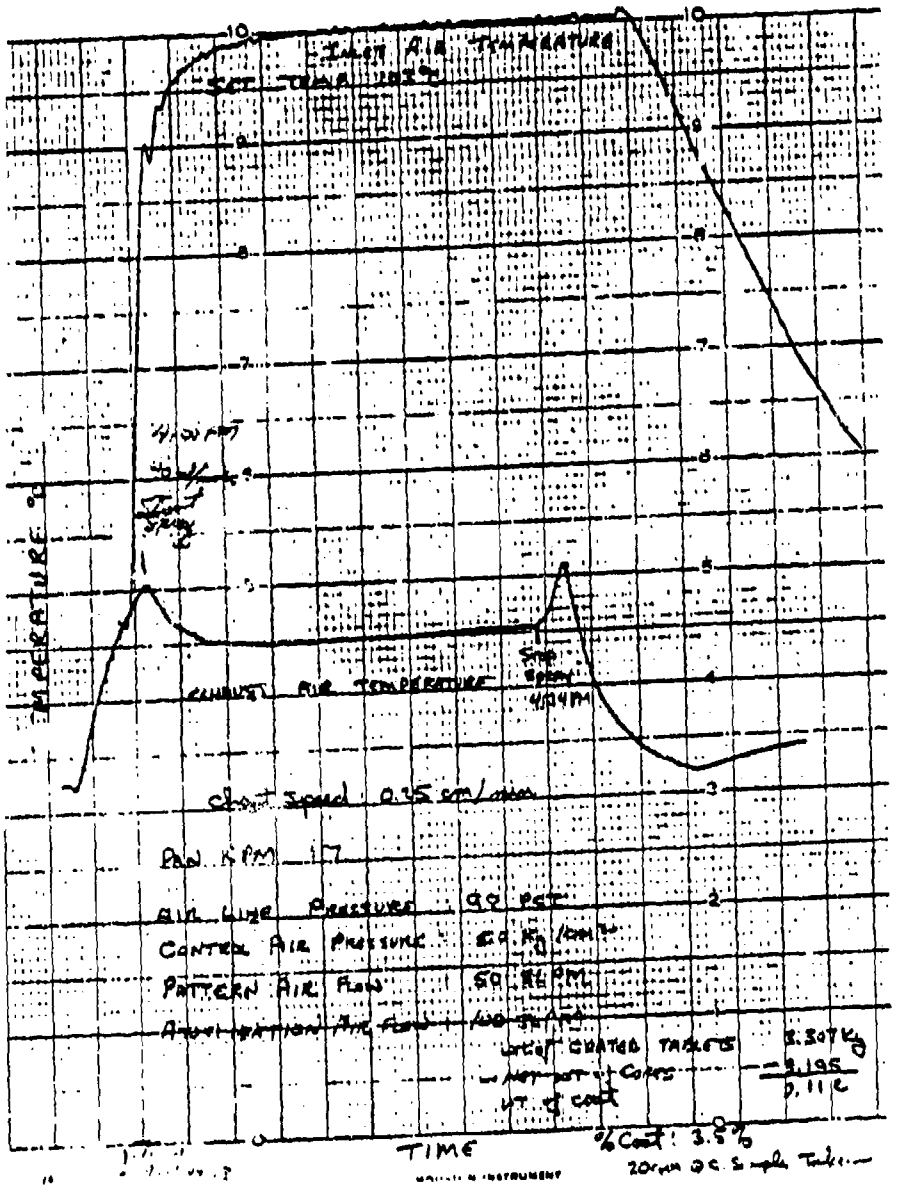
Coating Solution

Control No.

Special Instructions

CONTAINS	INGREDIENTS AND DIRECTIONS	RAW MAT'L CONTROL NO.	INITIAL	WEIGHT OF BATCH
	Add to a clean, stainless steel container			
	Water for Injection, USP	W3-059		4.400 kg.
	Mfr.: Utah Plant Facility			
	EDP #: 3540			
	Exp. Date: 2-24			
	Add slowly to the same container, with mixing			
	Mixing Started: 10 AM			
	Hydroxypropyl Methylcellulose, USP	Y-011-016		0.346 kg.
	5 cps			
	Mfr.: Dow Midland E.S. Plant			
	Mfr. Lot #: Dow 072732.6 (Lot 1111)			
	EDP #: 0996			
	Raw Material Lot #: 516-016-516			
	Exp. Date: 1-16-25			
	Polyethylene Glycol 400 N.F., N.F.	Y-011-019		0.024 kg.
	Mfr.: Union Carbide			
	Mfr. Lot #: 3166 15257 218			
	EDP #:			
	Raw Material Lot #: [illegible]			
	Exp. Date: 3-16-25			
	Mix until a uniform, clear solution is formed			
	Mixing Stopped: 12 PM			
	Timed By:			
	Let stand for at least 1 hour before use			
	Rest Time Started: 12 PM			
	Rest Time Stopped: 1 PM			
	Timed By:			
	Use this solution as coat			
	WRA-12-0401) Active Tablets 1.5 kg solution for 3.125 kg Cores			
	WRA-11-0401) Placebo Tablets 1.13 kg solution for 3.250 kg Cores			


INLET AIR TEMPERATURE
EXHAUST AIR TEMPERATURE
TEMPERATURE °C
AIR LINE PRESSURE : 95 PSI
CONTROL AIR PRESSURE : 60 m/cm²
PATTERN AIR FLOW : 60 SLPM
ATOMIZATION AIR FLOW : 100 SLPM
CHART SPEED 0.25 cm/MIN
TIME


INLET AIR TEMPERATURE
EXHAUST AIR TEMPERATURE
TEMPERATURE °C
TIME
Chart Speed 0.25 cm/min
Fan RPM 17
Air Line Pressure 90 PSI
Control Air Pressure
Pattern Air Flow 50 RE PM
% Coat: 3.5%
20 min @ C. Simple Tube

Sterile Water for Injection, U.S.P., PS #023-039

Test	Specification	Found
pH	USPXX NFXV 5.0 - 7.0	6.99 NE1-023-024
Chloride	USPXX NFXV <0.5 PPM	Met USP Requirements NE1-023-024
Sulfate	USPXX NFXV	Met USP Requirements NE1-023-024
Ammonia	USPXX NFXV	Met USP Requirements NE1-023-024
Calcium	USPXX NFXV	Met USP Requirements NE1-023-024
Carbon Dioxide	USPXX NFXV	Met USP Requirements NE1-023-024
Heavy Metals	USPXX NFXV	Met USP Requirements NE1-023-024
Oxidizable Substances	USPXX NFXV	Met USP Requirements NE1-023-024
Total Solid	USPXX NFXV <0.002%	Met USP Requirements NE1-023-024
Pyrogen Test	USPXX NFXV	Met USP Requirements TFC-N-089
Sterility Test	USPXX NFXV	Met USP Requirements TFC-TT-3

T. F. C.

Pharmaceutical Services
College of Pharmacy
The University of Iowa
Iowa City, Iowa 52242

8'1

Pharmaceutical Control Laboratory
College of Pharmacy

PYROGEN TESTING

EDP 3540 Department IV

Item Sterile Water for Injection U.S.P

Lot Number 023-039 Date Manufactured 02-11-83

Average Max. Temp. Increase 0.07

Notes 10ml to 1vial 20mg NaCl expir 10ml/1y

PYROGEN TEST:

Test No.	Rabbit No.	Weight before test	Placed in box (Time)	Normal temp. (Time)	Dose ml.	Temperature, control time in hours 0	1	2	3	4	Max. temp. change (-)	(+)
1	129	4.21	1 / 5:45	39.4 / 6:45	42.1	39.4	39.4	39.5	39.4		0	0.1
2	130	3.52	2 / 5:45	39 / 6:45	35.2	39	39	39'	39'		0	0.1
3	131	3.44	3 / 5:45	39' / 6:45	34.4	39'	39	39'	39'		0.1	0

RESULTS:

Test Results OK

Test by Mitchell Date 3-9-83

Control Number N-289

Approved by Supv Eng C Lin

Date 3-9-83

P-31

Pharmaceutical Control Laboratory
College of Pharmacy

STERILITY TESTING

PDF 9540 Cert ① Department IV

Item Sterile Water for Injection U.S.P.

Lot Number 023-094 Date Manufactured 02-11-83

Batch Size 890 L Date Submitted 2/16/83

STERILITY TEST:

Vol. Medium 80	Medium					
	Thioglycollate			Soy-Bean-Casein		
Inoculum 10	3 days	7 days	14 days	3 days	7 days	14 days
No. Tubes 40	OK	OK	OK	OK	OK	OK

RESULTS:

Date Started 2/16/83

Date Completed 3/2/83

Test by Jon M Mundt

Control Number TT-3

Approved by Linda Jorg RL

Date 3-2-83

Growth NA

No Growth ✓

Negative for NA

Control Qnal 24

Others NA

I-51

Pharmaceutical Control Laboratory
College of Pharmacy

STERILITY TESTING

RBP 3540 Cart @ Department IV

Item Sterile Water for Injection U.S.P.

Lot Number 023-034 Date Manufactured 02-11-83

Batch Size 890 L Date Submitted 2/14/83

STERILITY TEST:

Vol. Medium 80 ml	Medium					
	Thioglycollate			Soybean-Casein		
Inoculum 10 ml	3 days	7 days	14 days	3 days	7 days	14 days
No. Tubes 20	NL	NL	NL	NL	NL	NL

RESULTS:

Date Started 2/14/83

Date Completed 2/24/83

Test by Jan M Mundell

Control Number TT # 3

Approved by Ling-Ling Chi

Date 3-2-83

Growth NA

No Growth ✓

Negative for NA

Control Growth

Others NA

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College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4520

Hydroxypropyl Methylcellulose, USP, Lot #2432

PS # 526-016-526

Identification Test: Passed
Y-011-016
(Certificate of Analysis attached)

T. F. Chi

DOW CHEMICAL U.S.A.

POST OFFICE BOX 68511
9550 N. ZIONSVILLE ROAD
INDIANAPOLIS, INDIANA 46268
317 · 873-7000

January 15, 1981

John Lach, Ph.D.
University of Iowa
College of Pharmacy
Iowa City, Iowa 52240

Dear Dr. Lach:

Enclosed are the analytical reports for Methocel® E-5 Premium, lot D-2432, which was sent to you earlier. I hope the material was satisfactory for your experiments.

Sincerely,

Ken Bassler

Ken Bassler, Ph.D.
Sr. Research Pharmacist
Industrial Pharmacy

gh

ANALYTICAL REPORT

PKG. COMPONENT	PART NO.	DESCRIPTION
Container		
Closure		
Inner Seal & Glue Aid or Liner		
Other		

Copies K Basler

Comment

Charge No. 87166 05050

Date Pkg.

Pkg. Serv. Project No.

Product Methocel E-5 PH Ltd. Premium

Lot No. D-2432

Book No. HM077-5521 EL

Assay For:

Raw Material Spec.

Rqlk

Time Period and Samples

Reference	Test		Amt. Transferred		
BK1173198	Description	Pass			
1.3.5.5.90	LOD	2.497 gm/100 gm for 2 hr. Pass			
Spec. 1150	Viscosity	Interpoint - Within Limits			
		200 cps ± 20% - Satisfies Viscosity			

8-14-90

Date and Approval 8-17-90 Rqlk

I-10

ANALYTICAL REPORT

COMPONENT	PART NO.	DESCRIPTION
Liner		
Sure		
er Seal & e &/Or Liner		
er		

Copies S. Hawes

Comment

Charge No. 8 7126505030

Rpte Pkg.

Pkg. Serv. Project No.

Product METHOCEL ES PREMIUM

CAS Lot No. D-2432

IP Book No. MH07R21EL

Assay For: RAW MATERIAL SPECS

Lot 121

e Period and Samples

Reference	Test			Amt. Transferred	
No. F13-212		Pass			
S Rupp		Pass			
13,574					
	LOD				

I-11

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Iowa City, Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4520

Polyethylene Glycol 400, NF, Lot # 18257228

PS # 631-016-631

Identification Test: Passed
Y-031-119

(Certificate of Analysis Attached)

T. F. Chi

I-13

PLANT LABORATORY

PRODUCT QUALITY REPORT

UNION CARBIDE CORPORATION CHEMICALS AND PLASTICS

INSTITUTE PLANT
P.O. BOX 2031
CHARLESTON, W.VA. 25330

9-8-81

To: Mr. John Jordan
Univ. of Iowa
College of Pharmacy
Box 21
Iowa City, Iowa 52241

The analysis of CARBOWAX Peg400Sen shipped your company in ----, on ---, your order number not available our order number not available, is as follows:

Analysis, Batch or Lot No.	1525722B
No. of Cartons, Bags or Drums	---
Molecular Wt.	393
Ph 5% Solution	6.3
Water Solubility	Pass
Color, Pt.	18
Ash, % by wt.	
Clarity	Clear
Viscosity @ 210 deg. F, cks	7.2
Suspended Matter	SubFree
Water, % by wt.	
Odor	Pass
Mono-Diethylene Glycol, % by Wt.	0.04
Specific Gravity @ deg. C.	
Acidity @ HAc, % by Wt.	
Heavy Metals, ppm	Less 2
Arsenic, ppm	Less 1
Sulfated Ash, % by Wt.	0.00
Freezing Point, deg. C.	
Melting Point, deg. C.	
Ethylene Oxide % by Wt.	0.00

Laboratory Supervisor
Quality Assurance Laboratory
Institute Plant

Appendix II

Quality Control Tests for Coated WR142,490·HCl 250 Mg Tablets (Lot WRA-12-04013).

II-1

University of Iowa College of Pharmacy Page 1 of _____ pages

Form CP 1
1987

MANUFACTURING FORMULA

Product WR 142,490 AS HCl Tablets
Formula
Written by _____ Date _____ Checked by _____ Date _____
Formula
Production authorized by _____

Lot No. WRA-12
Batch Size 5,775
Control No. WRA-12-05013

Analysis

Assay for	Theoretical	Actual
These tablets were supplied by WRAIR to Pharmaceutical Services for coating only. They were manufactured by Lafayette Pharmaceutical, Inc. (Lot R-398). No content uniformity was carried out.		

Control Assay No. _____ Worksheet Checked by _____ Date _____

Specifications

	Initial	Theoretical	Actual
Size			
Weight (coated) See attached sheet		N/A	367 mg
Color			
Dimensions See attached sheet		N/A	9mm, Oval
Tablet Hardness			
Tablet Thickness			
Clarity			
pH			
Density			
Viscosity			
Sedimentation			
Gross Appearance of coated tablet		White tablet with clear film coat	Clear Pink Film Coat
ority			
Pyrogen			
Other Dissolution (See attached Sheet)		22.4% in 90 min. (uncoated)	36% in 60 min (coated)

Package and Label

Type of Container Amber glass vial with standard closure.
Size of Container 7 dram
Method of Packaging
PEI Versacount Tablet Counter

Remarks
25 tablets per vial.

Head space filled with Rayon Pharmaceutical Coil.

Packaged by _____
Date 4/21/89

WALTER REED ARMY INSTITUTE OF RESEARCH
Division of Experimental Therapeutics
Washington, D.C. 20307

WR 142,490 AS 200 mg 25 Tablets
(S,S)-trans-4-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthylidene]-2-butenylamine hydrochloride

Control No. WRA-12-05013
Manufactured 1/89 Caused by Date No 233
CAUTION: New Drug limited by Federal Law to Investigational Use Only
Manufactured by Pharmaceutical Services a College of Pharmacy a The University of Iowa a Iowa City, Iowa 52242

The University of Iowa
Iowa City, Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4820

WEIGHT VARIATION OF FINISHED TABLETS

Product: WR 142,490 AS HCl Tablets (coated)

Lot No.: WRA-12-04013

No.	mg/Tablet	No.	mg/Tablet
1	562	11	563
2	567	12	575
3	570	13	577
4	565	14	565
5	576	15	557
6	571	16	533
7	570	17	573
8	565	18	580
9	568	19	567
10	568	20	574

Average weight: 567 mg.

Deviation from low (533 mg) = 6.0 %

Deviation from high (580 mg) = 2.3 %

Control No.: WRA-121-043

T. F. Cohen

The University of Iowa
Iowa City, Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4520

1847

DISINTEGRATION TEST

Product: WR 142,490 AS Tablets

Lot No.: WRA-12-04013

Apparatus: USP XX, p. 958

Medium: 900 ml simulated gastric fluid

Temperature: 37°C.

Test: 4 minutes and 55 seconds

Control No.: WRA-122-053

T. F. C

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Iowa City, Iowa 52242

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Department of Pharmaceutical Service

(319) 353-4520

DISSOLUTION

Product: WR 142,490 AS, 250 mg.
Lot No.: WRA-12-04013

Apparatus: USP XX, dissolution apparatus 1, p. 959
Medium: 900 ml 0.1N HCl
Temperature: 37 ± 0.5°C.
Speed: 50 rpm
Dilution: 2 ml 10 ml with distilled water

I.	Time (min)	% Dissolved
	30	14.66
	60	29.84
	90	41.07

II.	Time (min)	% Dissolved
	30	9.11
	60	22.06
	90	31.70

III.	Time (min)	% Dissolved
	30	11.75
	60	26.54
	90	38.16

IV.	Time (min)	% Dissolved
	30	12.02
	60	29.49
	90	36.05

V.	Time (min)	% Dissolved
	30	16.11
	60	27.60
	90	38.82

VI.	Time (min)	% Dissolved
	30	8.85
	60	25.36
	90	38.96

Control No.: WRA-123-053

T. F. Chi

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Department of Pharmaceutical Service

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APPROVAL FOR SHIPMENT FORM

Product Name: WR142-490AS HCL 250 mg.

Lot Number: WRA-12-04013

Container Size: 25 tablets

Dosage Form: Tablets

Acceptable Container: 231

Rejects: 0

Total Units Shipped: 231

Date Shipped: 25 April 1983

Name and Address of Receiver:

Dr. Larry Fleckenstein

Forest Glen Annex; Bldg 500; Brookville Rd.

Walter Reed Army Institute of Research

Silver Spring, MD 20910

Approval of Shipment by: J. Jacobs RPh.

Appendix III

Manufacturing Formula and Quality Control Tests on WR142,490·HCl Placebo Tablets (Lot WRA-13-04013).

...ity of Iowa College of Pharmacy Page 1 of _____ pages

Form CP 1
1/69

MANUFACTURING FORMULA

Product: Placebo Tablets for WR 142,490 HCl	Lot No. WRA-13
Formula Written by: [illegible] Date: 4/16/81 Formula Checked by: [illegible] Date: 4/16/81	Batch Size 10,000
Production corrected by: [illegible]	Control No. WRA-13-04013

Analysis

Assay for	Theoretical	Actual
WR 142,490 HCl	Undetermined	[illegible]

Control Assay No. _____ Worksheet Checked by _____ Date _____

Specifications

	Limit	Theoretical	Actual
Size		7/16-inch S.C.	7/16-inch S.C.
Weight (Uncoated) (See attached sheet)		392.2 ± 22.4 mg.	393 mg
Color (Uncoated)		White	White
Disintegration (See attached sheet)		NMT 30 minutes	[illegible]
Tablet Hardness (See attached sheet)		[illegible]	[illegible]
Tablet Thickness (See attached sheet)		3.8 ± 0.5 mm.	[illegible]
Clarity			
pH			
Density			
Viscosity			
Sedimentation			
Appearance of Coated Tablet		White tablet with [illegible]	[illegible]
Sterility			
Pyrogen			
Other Weight Variation (Uncoated)		NMT [illegible]	[illegible]

Package and Label

Type of Container: Amber glass vial w/std. [illegible]
Size of Container: 1 dram CLOSURE
Method of Packaging:
PEI Versacount Tablet Counter

Remarks:
25 Tablets per Vial

Read space filled with Rayon Pharmaceutical cell

Packaged by [illegible] 4/22/81

WALTER REED ARMY INSTITUTE OF RESEARCH
Division of Experimental Therapeutics
[illegible]
[illegible] Placebo [illegible] Tablets
[illegible] Date No. 170
[illegible]

Page ____ of ____ pages

Product Placebo Tablets for VB 162,490 HCl List No. VBA-13

Batch Size 10,000 Control No. VBA-13-0401?

Caution or Special Instructions

1907

EACH CONTAINS	INGREDIENTS AND DIRECTIONS	RAW MAT'L CONTROL NO.	INITIAL	AMOUNT PER BATCH
421.2 mg.	1. Welsh Lactose USP Anhydrous.	AA-071-007		4.21 kg.
60.0 mg.	2. Welsh Avicel PH 101.	HH-013-124		600 gm.
55.0 mg.	3. Welsh Sta-Rx 1500.	W-010-011		550 gm.
	4. Blend Lactose, Avicel and Sta-Rx in a V-blender for 10 minutes.			
3.3 mg.	5. Welsh Magnesium Stearate and transfer it to the V-blender (4).	SS-042-014		33 gm.
	6. Blend it for 5 minutes.			
11.0 mg.	7. Welsh Talc and transfer it to the same V-blender (4).	HH-MA-009		110 gm.
	8. Blend it for an additional 5 minutes.			
	9. Compress on single punch tablet machine (Manesty) using 7/16-inch S.C. (standard concave) punch and die set. Monitor tab/wt weight (5.52 gm for 10 tablets), hardness (2 a kp.) and thickness.			
	10. Vacuum tablets, inspect and package.			
	11. Package 25 tablets in 7 dram amber glass vials using Veraseal automatic filling machine.			
	12. Yield:			
	Total weight of the finished product: 8.35 kg.			
	(Net wt of waterfill bottle filled): 8 kg. 1/2 bottle			
	Total # of bottles filled: 317			
	# of Tabs/bottle: 25			
	Total # of dram packaged: 7,925 Tabs			

Page ____ of ____ page

Product .. Placebo Tablets (for HR 16,690 HCl) ____ List No. ___VBA-13____

Batch Size ___10,000___ Control No. ___VBA-13-040(1)___

Caution or Special Instructions

1307

EACH CONTAINS	INGREDIENTS AND DIRECTIONS	RAW MAT'L CONTROL NO.	INITIAL	AMOUNT PER BATCH
	IN-PROCESS CONTROL			
	Weight (5.10-5.40 gm. for 10 tablets) / Hardness (4 - 6 kp) / Thickness (3.1-3.3 mm)			
	372 / 5.4-6 / 3.25			
	365 / 5.1-6 / 3.23			
	367 / 5.2-6 / 3.24			
	368 / 5.1-5.9 / 3.23			
	366 / 5.1-5.9 / 3.24			
	365 / 5.0-6.1 / 3.24			
	369 / 5.4-6 / 3.24			
	370 / 5.4-5.8 / 3.24			
	370 / 4.9-5.9 / 3.23			
	371 / 5.0-5.8 / 3.24			
	359 / 4.1-4.4 / 3.25			
	Av. 5.42 Av. 3.24 mm			

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Department of Pharmaceutical Service

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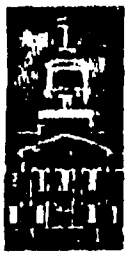

IN-PROCESS CONTROL

Product: Placebo Tablet for WR 142,490 HCl

Lot No.: WRA-13-04013

Quantitative Analysis: WR 142,490 HCl wasn't detected

Control No.: WRA-053-133

T. F. Chiu

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Iowa City, Iowa 52242

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Department of Pharmaceutical Service

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1847

WEIGHT VARIATION OF FINISHED TABLETS (Uncoated)

Lot No.: WRA-13-04013

No.	mg/Tablet	No.	mg/Tablet
1	567	11	564
2	566	12	560
3	570	13	570
4	555	14	563
5	570	15	566
6	560	16	559
7	565	17	553
8	553	18	555
9	573	19	560
10	570	20	562

Average weight: 563 mg/Tablet

Deviation from low (553 mg) = 1.8%

Deviation from high (573 mg) = 1.7%

Control No.: WRA-130-043

T. F. Chen

The University of Iowa
Iowa City, Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4820

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WEIGHT VARIATION OF FINISHED TABLETS (COATED)

Product: Placebo tablets for WR 142,490 HCl

Lot No.: WRA-13-04013

No.	mg/Tablet	No.	mg/Tablet
1	590	11	578
2	580	12	592
3	575	13	579
4	586	14	583
5	587	15	585
6	580	16	590
7	583	17	596
8	579	18	579
9	584	19	591
10	588	20	587

Average weight: 585 mg/Tablet

Deviation from low (575 mg) = 1.7%

Deviation from high (596 mg) = 1.9%

Control No.: WRA-131-043

T. F. C Lui

The University of Iowa
Iowa City, Iowa 52242

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Department of Pharmaceutical Services

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DISINTEGRATION TEST

Product: Placebo Tablet for WR 142,490 HCl (Coated)

Lot No.: WRA-13-04013

Medium: 900 ml distilled water

Temperature: 37°C.

Apparatus: USP XX, p. 558

Time: 13 minutes

Control No.: WRA-132-053

I. F. Chen

The University of Iowa
Iowa City, Iowa 52242

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Department of Pharmaceutical Service

(319) 353-4620

Lactose U.S.P. Anhydrous, Lot # INF09

PS # M819-016-819

Identification Test: Passed
AA-071-007

(Certificate of Analysis Attached)

T. F. C.

SHEFFIELD PRODUCTS — PROTOCOL OF ASSAY

819-016-819

CUSTOMER: UNIVERSITY OF IOWA
ADDRESS: PURCHASING DEPT
IOWA CITY IOWA 52242

ATTN PURCHASING

PRODUCT: LACTOSE U.S.P. ANHYDROUS DIRECT TABLETING
LOT NO.: INF89
CUSTOMER ORDER NO.: [redacted] W0371

DATE SHIPPED: 6/24/81
NUMBER OF DRUMS: 3
INVOICE NO.: 72498

RESULTS OF ASSAY WHERE APPLICABLE TO PRODUCT SHIPPED:

CHEMICAL/PHYSICAL		MICROBIOLOGICAL	
SOLUBILITY	PASS	STAND. PLATE COUNT	<100/GRAM
MOISTURE %	0.54 - 0.54	THERMOPHILE COUNT	
ASH %	0.052	COLIFORM	NEGATIVE
HEAVY METALS	<5 PPM	SALMONELLA	NEGATIVE
SPECIFIC ROTATION	55.05	MOLD	<50/GRAM
ACIDITY	PASS		
PH E10% SOL.]	4.1 - 4.8		
ALCOHOL SOL. RESIDUE	2.77		

: This copy for your files

RECEIVED
JUN 29 1981
PURCHASING DEPT

DATE: 6/24/1981

SHEFFIELD PRODUCTS, BOX 398, MEMPHIS, TENN. 38101 KRAFT INC.

The information herein is true & accurate to the best of our knowledge. However, both the information & product are offered without warranty or guarantee as to any specific use. Nothing herein shall be construed as a recommendation to use any product in violation of any patent rights.

The University of Iowa
Iowa City, Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4520

Avicel PH 101, FMC, Lot 1301

PS # M988-017-988

Identification Test: Passed
MH-023-124

(Certificate of Analysis Attached)

T. F. C

III-11

FMC CORPORATION
Food & Pharmaceutical Products Division
1301 Ogletown Road
Newark, Delaware 19711

PRODUCT QUALITY CONTROL REPORT

PRODUCT: AVICEL PH-101
Microcrystalline Cellulose, N.F.

LOT NO: 1301
DATE : 1/10/83

Identification	Conforms to NF XV
Loss on Drying, %	3.6 - 4.1
Heavy Metals, ppm	<10
Residue on Ignition, ppm	45
Water Soluble Substances, mg/5g	4.5
Particle Size, WT. % + 60 mesh	<0.1
WT. % + 200 mesh	15 - 23
pH	6.1
Assay, % cellulose	98.8
Starch Test	negative
Retained on a screen having 37 um openings, wt. %	>5
Identification	passes

R. B. Worth SN.

R. B. Worth
Quality Control Manager

The University of Iowa
Iowa City, Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4820

Sta-Rx 1500 Starch, Lot No.: 905029

PS # M275-016-275

Identification Test: Passed
W-060-061

(Certificate of Analysis Attached)

T. F. Chiu

COLORCON INC. 2117 N. GALE STREET · INDIANAPOLIS · INDIANA 46211
(317) 545-6211

STA-RX 1500 STARCH PROTOCOL

BATCH NO: 905029

DATE OF REPORT 4/16/80

ANALYTICAL DATA:

Loss on drying	10.6%
Residue on ignition	0.12%
Iron	<10ppm
pH	5.6
Oxidizing Substances	NEG
Sulfur Dioxide	OK

Microbial Limits:

Standard Plate Count, per g	<10
Mold, per g	<10
Yeast, per g	<10
Salmonella	NEG
E. Coli	NEG
Psudomonas Aeruginosa	NEG
Coagulase Positive Staphylococcus Species	NEG

Screen Analysis:

On U.S. No: 8, %	0.0
On U.S. No: 40, %	0.01
Through U.S. No:100, %	93

Cold Water Solubles, % d.s.b. 11.7

APPROVED FOR SHIPMENT BY G.A. Hunter
COLORCON, INC.

The University of Iowa
Iowa City, Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4520

Magnesium Stearate, N.S., Mallinckrodt Lot KMSZ

PS # M 364-017-364

Identification Test: Passed
DD-042-096

(Certificate of Analysis Attached)

T. F. Chi

Mallinckrodt, Inc.

PARIS BY-PASS • PO BOX M • [illegible] • [illegible]

ITEM - MAGNESIUM STEARATE NF CODE 2256

LOT KMSZ

TESTS	RESULTS
Identification	Passes test.
Loss on drying	3.64%
Lead (Pb)	less than 0.0001%
Assay (MgO)	7.7%
Sieve test US Standard #325 Mesh	99.6% thru

It is hereby certified that the above is a true copy of the actual analysis of the subject item.

Ted Dubowski
Manager Quality Control
Mallinckrodt, Inc.
Paris, Kentucky

js 7-8-82

The University of Iowa
Iowa City Iowa 52242

College of Pharmacy
Department of Pharmaceutical Service

(319) 353-4820

Talc USP, Lot # 491-C

PS # M868-017-868

Identification Test: Passed
MR-122-004

(Certificate of Analysis Attached)

T. F. C

Cyprus Industrial Minerals Company
Talc Division

566 South Flower Street
Los Angeles, California 90071
Telephone (213) 489-3700

TWX (910) 321-3753

po# Y 61315-RARICK
lot# 491-G
002-20590

Thompson [illegible]rd Chemical Company
4330 Geraldine Avenue
St. Louis, Missouri 63115

Gentlemen:

We certify that Supreme USP/Supreme USP Dense, Lot Number 491-G, shipped to you on your purchase order ----- meets or exceeds the specifications for USP Talc. A copy of these specifications is attached. We also certify that this material is free of any detectable asbestos as measured by X-Ray Diffraction techniques.

Sincerely,

C. R. Moebus
Vice President
Technical Services

CRM:mc

Attachment

CC: JSF

TALC

Talc is a native, hydrous magnesium silicate, sometimes containing a small proportion of aluminum silicate.

Description: Very fine, white or grayish white, crystalline powder. Is unctuous, adheres readily to the skin and is free from grittiness.

Identification—Mix 500 mg. with about 200 mg. of anhydrous sodium carbonate and 2 g. of anhydrous potassium carbonate, and heat the mixture in a platinum crucible until fusion is complete. Cool, and transfer the fused mixture to a dish or beaker with the aid of about 50 ml. of hot water. Add hydrochloric acid to the liquid until effervescence ceases, then add 10 ml. more of the acid, and evaporate the mixture on a steam bath to dryness. Cool, add 20 ml. of water, boil and filter the mixture: an insoluble residue of silica remains. Dissolve in the filtrate about 2 g. of ammonium chloride, and add 5 ml. of ammonia T.S. Filter if necessary, and add sodium phosphate T.S. to the filtrate: a white, crystalline precipitate of magnesium ammonium phosphate separates.

Loss on ignition—Weight accurately about 1 g. and ignite at red heat* to constant weight: it loses not more than 5 percent of its weight.

Acid-soluble substances—Digest 1.00 g. with 20 ml. of diluted hydrochloric acid at 50° for 15 minutes, add water to restore the original volume, mix and filter. To 10 ml. of the filtrate add 1 ml. of diluted sulfuric acid, evaporate to dryness, and ignite to constant weight: the weight of the residue does not exceed 10 mg. (2 percent as sulfate).

Reaction and soluble substances—Boil 10 g. with 50 ml. of water for 30 minutes, adding water from time to time to maintain approximately the original volume, and filter. The filtrate is neutral to litmus paper. Evaporate one-half of the filtrate to dryness; and dry at 105° for 1 hour: the weight of the residue does not exceed 5 mg. (0.1 percent).

Water-soluble iron—slightly acidify with hydrochloric acid the remaining half of the filtrate obtained in the test for Reaction and soluble substances, and add 1 ml. of potassium ferrocyanide T.S.: the liquid does not acquire a blue color.

Packaging and storage—Preserve in well-closed containers.

CATEGORY: Dusting powder.

* i.e. 800° ± 25°F.

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Department of Pharmaceutical Service

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1847

APPROVAL FOR SHIPMENT FORM

Product Name: PLACEBO FOR WR142-490AS HCL

Lot Number: WRA-13-04013

Container Size: 25 tablets

Dosage Form: Tablets

Acceptable Container: 360

Rejects: 0

Total Units Shipped: 360

Date Shipped: 25 April 1983

Name and Address of Receiver:

Dr. Larry Fleckenstein

Forest Glen Annex; Bldg 500; Brookville Rd.

Walter Reed Army Institute of Research

Silver Spring, MD 20910

Approval of Shipment by: [signature] R.Ph.

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